MEDICAL LIBRARY

JAN 20 1950

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY DECEMBER 31 1949

TABLE OF CONTENTS

A Quantitative Approach to the Study of Transplantable Tumours
JAMES CRAIGIE, O.B.E., F.R.S. 1485

Anticoagulant Therapy H. W. FULLERTON, M.D., F.R.C.P., and G. ANASTASOPOULOS, M.D. 1492

Excretion of Chorionic Gonadotrophin by Pregnant Diabetics
J. A. LORAINE, M.B., M.R.C.P.Ed. 1496

Vitamin A, Total Carotenoids, and Thymol Turbidity Levels in Plasma
DOROTHY ADAMS CAMPBELL, M.B., B.S., and EVA L. TONKS, M.SC. 1499

Chloramphenicol in Infantile Gastro-enteritis
K. B. ROGERS, M.D., S. J. KOEGLER, M.D., and JOHN GERRARD, B.M., M.R.C.P. 1501

Paratyphoid B Fever Treated with Chloramphenicol
MICHAEL CURTIN, M.D., M.R.C.P.I. 1504

Diffraction Methods of Measuring Red Cell Diameters
ALAN J. HIRD, M.B., M.R.C.P. 1506

Two Successful Resections for Carcinoma of Pancreas HAROLD DODD, Ch.M., F.R.C.S. 1509

MEDICAL MEMORANDA

Hernia Through Foramen of Winslow. JOSEPH N. LEWIS, M.B., B.Ch. 1511
Treatment of Megaloblastic Anaemia with Vitamin B_{12}. C. M. MILLER, M.D., M.R.C.P., and E. H. MOORHOUSE, M.R.C.S., L.R.C.P. 1511

REFRESHER COURSE

Analgesia in Childbirth. C. LANGTON HEWER, M.B., M.R.C.P., F.F.A. R.C.S. 1521

GENERAL ARTICLES AND NEWS

Treatment of Pulmonary Tuberculosis with Para-aminosalicylic Acid and Streptomycin 1521
BRITISH ORTHOPAEDIC ASSOCIATION 1524
STAFF COLLEGE FOR HOSPITAL ADMINISTRATORS 1525
New Type of Vaginal Support. DAVID L. ARNOLD, D.R.C.O.G. 1525
MEDICO-LEGAL 1534
MEDICAL NOTES IN PARLIAMENT 1535
UNIVERSITIES AND COLLEGES 1536
MEDICAL NEWS 1536
BIRTHS, MARRIAGES, AND DEATHS 1537
QUESTIONS AND COMMENTS 1539

REPORTS OF SOCIETIES

ROYAL SOCIETY OF MEDICINE: Some Aspects of Undernutrition 1526
DEVON AND EXETER MEDICO-CHIRURGICAL SOCIETY: Epidemiological Research on Virus Diseases 1526

LEADING ARTICLES

PAS and Streptomycin 1515
Virus Theory of Cancer 1516
Short Oesophagus and Hiatus Hernia 1517

ANNOTATIONS

Pregnancy in Diabetics 1518
Animal Experiments 1518
Medical Practices Advisory Bureau 1519
Vitamin C and Benzene Poisoning 1520
Pain of Visceral Origin 1520
Medicine, 1900–50 1520

REVIEWS

Problem of Laboratory Animals 1513
Grading Muscular Function 1513
Freud: A Fresh Translation 1513

SUPPLEMENT

The Secretary Reports 275
Health Service.—REPORT ON MEDICAL CERTIFICATES — REMUNERATION OF MEDICAL OFFICERS IN THE ARMED FORCES—CHANGES OF DOCTOR—HOSPITAL MANAGEMENT COMMITTEES—GENERAL PRACTITIONERS' REMUNERATION 276
Remuneration of Officers of the Colonial Medical Service 278
QUESTIONS ANSWERED 277
WHITLEY MACHINERY IN PUBLIC HEALTH 281
LONDON ASSOCIATION FOR HOSPITAL SERVICES 281
CORRESPONDENCE 282
ASSOCIATION NOTICES 282

CORRESPONDENCE

Colour Plates. M. C. G. ISRAELS, M.D. 1527
Hormones and Rheumatism. WILLIAM HUGHES, M.D. 1527
Failed Forceps. A. P. BENTALL, M.B.; AUSTEN H. HOLMES, F.R.C.S.Ed.; G. GORDON LENNON, Ch.M.; R. E. FFRENCH DEVITT, L.R.C.P.I. 1528
Operative Treatment of Varicose Veins. HAROLD DODD, F.R.C.S. 1528
New Mechanism of Vitamin Deprivation. P. ELLINGER, M.D. 1529
Vagotomy for Peptic Ulcer. J. THOMSON SHIRLAW, M.D. 1529
Aureomycin in the Treatment of Pneumonia. M. KENIG, M.D. 1529
Pathological Fracture Treated by Methyl Testosterone. S. G. NARDELL, F.R.C.S. 1530
Stability of Society. JOHN TESTER 1530
Sign of Ruptured Ectopic Gestation. MORTIMER REDDINGTON, F.R.C.S. 1530
Points from Letters 1531

OBITUARY

Sir Charles Gordon-Watson, K.B.E., C.M.G., F.R.C.S. 1531
Lancelot Bromley, M.Ch., F.R.C.S. 1532
W. K. McKinstry, M.R.C.S. 1533
Mina L. Dobbie, M.D. 1534
J. K. Dunlop, M.B. 1534
Theodore A. W. Ogg, M.D. 1534
William Anderson, O.B.E., F.R.C.S. 1534
L. A. Humphrey, M.R.C.P. 1534

Epidemiology Section 1538

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4643, WEEKLY, PRICE 1/6

Copyright

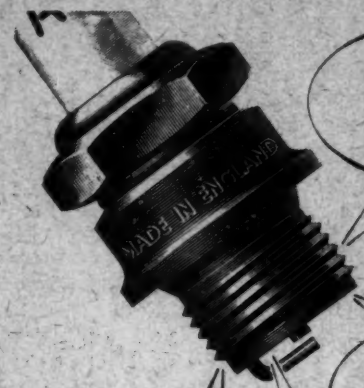
REGISTERED AS A NEWSPAPER

PERNICIOUS ANAEMIA— Treatment

Many years experience has shown that relatively small quantities of 'OXOID' Liver Extract (I.M.) will give entirely satisfactory results, frequent injection being unnecessary.

Potency of each batch is clinically determined before issue, as this is the only reliable method of standardising the dosage required to produce a satisfactory rate of increase in the red blood corpuscles.

'OXOID' Liver Extract (I.M.) is supplied in:
Ampoules—2 cc.
Bottles—10 cc. and 20 cc.



MORE MILES PER GALLON

QUICK, CERTAIN STARTING

WITH AIRCRAFT INSULATOR

MADE BY GENERAL MOTORS

AC SPARK PLUGS

AC-SPHINX SPARK PLUG CO. DIVISION OF GENERAL MOTORS LTD. DUNSTABLE, ENGLAND

'Semprolia'
D.D.T.
HAIR EMULSION

...a new effective treatment for head lice...

A new formula Hair Emulsion, containing D.D.T. as the active ingredient, for control of head lice. Pleasantly perfumed and simple to use. Apply by massaging into the scalp. No combing is required except for the removal of dead lice. Treatment is economical—individual application four drachms only. Sample, details of packages for clinical use and home treatment and prices on application.

ALSO STILL RECOMMENDED
'Semprolia' BRAND
MEDICATED (LETHANE) HAIR OIL N.W.F.

STEMCO LTD., 128 Albert St., Camden Town, N.W.1
Agents in Eire—May Roberts (Ireland) Ltd., Grand Canal Quay, Dublin

THE COLLECTOR'S BOOK CLUB

Specializes in limited modern first editions, superbly bound in full leather, blocked in real gold-leaf.
Prices from 12/6.

Members make their own selection from our lists.
There is a wide choice of important books every month, produced in co-operation with leading publishers and simultaneously with their first editions.

You need not take your books regularly.
There is no membership fee.

Become a member by pre-paying books of your own choosing to the value of five pounds (plus five shillings for postage).

Please write for our free prospectus to:
editions de luxe ltd., "Museum House" 25, Museum Street London, W.C.1 Tel: MUSEUM 1872

FINANCE

for the acquisition by

PAYMENTS OUT-OF-INCOME

of

SURGERY AND OTHER FURNITURE, SURGICAL INSTRUMENTS, MEDICAL TEXT BOOKS, X-RAY APPARATUS, MOTOR CARS

The above list is illustrative only. Under its equipment Purchase Plan, the company is prepared to assist doctors to acquire ANY article and spread the cost over a period.

BRITISH MEDICAL FINANCE LTD.

Tavistock House South, Tavistock Square, London, W.C.1.

NEW TEXTBOOKS for STUDENTS and PRACTITIONERS
preparing for the Higher Examinations

HANDBOOK OF MEDICINE FOR FINAL YEAR STUDENTS
by G. F. WALKER, M.D., M.R.C.P., D.C.H.
This well-known book has been completely revised and brought up to date. Previous editions have met with an enthusiastic reception. Valuable for M.R.C.P. and other higher examinations. *4th Edition. Pp.* 305. *Price*, 25s. net.

HANDBOOK OF MIDWIFERY
by MARGARET PUXON, M.D., M.R.C.O.G.
Specially useful for the D.R.C.O.G., M.R.C.O.G., etc. Just published. *Pp.* 326. *Price*, 25s. net.

HANDBOOK OF VENEREAL INFECTIONS
by R. GRENVILLE-MATHERS, M.A., M.D.Cantab.
An exposition of modern treatment by Penicillin. Valuable for specialists in this field. *Pp.* 116. *Price*, 12s. 6d. net.

HANDBOOK OF OPHTHALMOLOGY
by J. H. AUSTIN, M.B., D.O.M.S., D.O.Oxford.
Intended for candidates preparing for the D.O.M.S. and D.O. Examinations. *Just Published. Pp.* 340. *Price*, 30s. net.

Order now from all Medical Booksellers or direct from the Publishers.

SYLVIRO PUBLICATIONS, LTD.
19, Welbeck Street London, W.1

BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 31 1949

A QUANTITATIVE APPROACH TO THE STUDY OF TRANSPLANTABLE TUMOURS*

BY

JAMES CRAIGIE, O.B.E., F.R.S.

A period of intense experimental activity was ushered in when it was discovered, at the end of the last century, that some rat and mouse tumours could be transplanted. The discovery was made by Hanau, in Germany, and Moreau, in France, and was confirmed by Loeb and by Jensen. The significance of the introduction of the simple technique of tumour transplantation is that it removed a limitation that had greatly impeded progress, the limitation of the study of a tumour to the animal in which it had arisen. With the means of indefinitely prolonging the life of a tumour available, experimental oncology developed rapidly. Much substantial progress was made, but many hopes remained unfulfilled or were proved to be built on imperfect knowledge and misunderstanding of the available facts. I make reference to these disappointments because I feel that the title of this lecture may perhaps suggest an undue and unwarranted degree of optimism about the amount of useful information that remains to be gathered by transplanting tumours from one animal to another. There are many lessons in the mistakes and disappointments of the early period of study of transplantable tumours which should not be forgotten in the conduct of any branch of cancer research.

A number of important facts emerged from the work of Loeb, Jensen, Borrel, Ehrlich, Apolant, Bashford, Murray, Haaland, Woglom, and others on transplantable tumours. Those which are relevant to my subject may be summarized very briefly.

Serial passage of a tumour is possible only in the species in which it arises, and within the species is usually restricted to animals of the same genetic constitution. The importance of genetic background is due to the fact that transplantation is dependent on the inoculation of living tumour cells which, since they retain genetic characteristics of the original host, are rejected by a genetically alien one. A pedigree of tumour cells remains unbroken throughout the history of transplantation of the tumour. Each successive host provides anew at each transplantation the vascular supply and stroma necessary for continued growth of the tumour. There are of course exceptions to this continuity of cell pedigree. The carcinogenic viruses—namely, the Rous and other avian viruses, the Shope papilloma virus, and others—will produce tumours *de novo* by infection of cells of the host. Again, a transplantable carcinoma may sometimes be replaced by a sarcoma, or a tumour specific for one inbred strain of mice may acquire the ability to grow in other strains. Nevertheless, the essential facts I have mentioned apply to the vast majority of transplantable tumours.

*Imperial Cancer Research Fund Lecture given at the Royal College of Surgeons of England on November 22.

Transplantation Technique

When tumour transplantation is practised merely as an adjunct to other studies which require that the life of a tumour be extended artificially over a series of generations of the host animal, a comparatively simple yet necessarily aseptic technique suffices. Small fragments may be cut from the parent tumour and introduced singly to the desired sites in new hosts by a wide-bore needle or trocar and cannula. Alternatively the tumour may be reduced to an emulsion by mincing with scissors or a special instrument, or pounding it with a pestle in a mortar. Saline or Ringer's solutions are used only when it is necessary to thin the emulsion so that it can be injected to special sites by means of a fine needle. The graft or emulsion is usually placed subcutaneously, but other sites are employed for special purposes.

For the purposes for which they were designed and continue to be used, these simple transplantation techniques have the merit of combining simplicity with adequacy. The tumour cells are transplanted to their new hosts with a minimum of delay, and by using finely divided emulsions similar amounts of tumour cells can be inoculated into each animal of a group.

Various arguments might be advanced to justify an attempt to develop more quantitative methods for special purposes. On the other hand, consideration of the nature of the phenomena involved when a portion of living tumour tissue is transplanted to a new host and the extent to which the rate of growth may vary might lead to the conclusion that transplantable tumours are unlikely to be amenable to quantitative investigation. In view of the many obvious practical difficulties that have to be faced I do not feel justified in speculating on the possible practical applications of non-existent methods. However, it would seem desirable to indicate my main purpose in attempting to approach the study of transplantable tumours from a quantitative viewpoint.

The Quantitative Point of View

Numerous authors, arguing from the existence of a number of carcinogenic viruses, have suggested that many mammalian tumours, if not all, may be of virus aetiology. Failure to demonstrate viruses in tumours which cannot be propagated except by transplantation has been attributed to technical limitations and low transmissibility of the virus

from tumour to normal cells. Many excuses for failure to transmit transplantable tumours with cell-free filtrates, or with preparations from which living cells cannot be excluded with certainty, could be advanced in the light of our present-day knowledge of viruses. All the carcinogenic viruses amenable to conventional techniques have, so to speak, been dragged out into daylight. Yet hypotheses invoking the existence of more elusive ones can be advanced and cannot be disproved experimentally. Thus even the most sceptical must admit that there is a virus problem in relation to cancer, if only in this form.

So far as transplantable tumours are concerned I do not think that any real progress can be made with this problem until an adequate foundation of quantitative data has been laid down. It is necessary to determine, for example, using a representative series of selected tumours, the relationship between the dose of living tumour cells inoculated and the rate at which a tumour is produced at the site of inoculation. It is also urgently necessary to discover to what extent tumour cells can survive under various environmental conditions *in vitro*. I believe that it is only against an adequate background of such knowledge that we can obtain evidence for or against the existence of carcinogenic viruses of low transmissibility to normal cells. The evidence for or against will inevitably emerge without being directly sought for if a sufficiently complete quantitative characterization of tumour transplantation phenomena becomes possible.

However, for the moment it does not seem to be necessary to aim directly along such lines at such a distant objective as complete resolution of the virus problem. Indeed, it would be foolish to do so, for there are many important things that we do not know about the nature of viruses, as current speculations indicate clearly enough (vide Bauer, 1949). There seem to be ways in which quantitative refinements might be usefully introduced into investigations in which transplantable tumours are employed. If quantitative methods can be developed to the point of practical usefulness we may be confident that some information will accumulate which will be relevant to the virus problem in cancer.

Essential Specifications

Let us consider the three essential specifications that must be complied with if adequate quantitative methods are to be realized.

1. The preparations of tumour cells used for inoculation must be sufficiently homogeneous to obviate significant variations in the number of viable cells in different samples of a given volume of any given dilution.

2. The viability of the cells must be maintained unaltered during the period elapsing between the preparation of the inoculum and the completion of inoculation. This is a minimum requirement. It is obvious that opportunities for the development of quantitative techniques will depend on the period of time over which the activity of a suspension remains constant within the limits of error of determination of its activity. Should it be possible to reduce these limits of error to a level at which comparative titrations would be worth while, preliminary titrations would be necessary in order to narrow the range of cell concentrations and limit the number of animals used in the test proper. However, such two-stage tests will remain impracticable until methods of long-term stabilization of cell viability become available.

3. The third essential requirement is a quantitative method of comparing the activities of different tumour preparations.

The first specification presents a relatively simple problem which has been satisfactorily solved for present needs. Some progress has been made in regard to the second, and it has become clear that the viability of tumour cells may be extended for longer periods than might be expected from *a priori* considerations. The third requirement, a method of quantitative estimation, presents extremely difficult problems, which must await the accumulation of enough experimental data, and I would like this opinion to be borne in mind when, a little later on, I indicate one possible approach to the problem.

So far as is possible, I am going to present the progress of attempts to meet these specifications in a chronological manner. As will be appreciated, technical limitations and the experimental findings resulted, several times, in marked deviations from the more logical course that is obvious in retrospect. For example, if equipment for phase microscopy had been available when the work started just two years ago, or when dextrose was adopted as an aid to low-temperature preservation, the course pursued might have been very different.

Tumour Survival in Frozen State

The greater part of the work has been carried out with a mouse sarcoma (C3H, R.T., Ludford) which arose by stromal transformation of a sporadic mammary carcinoma. However, the initial attempts to preserve tumour-cell suspensions in the frozen state were made with a similar sarcoma of the R III strain (Ludford and Barlow, 1945). This tumour grows luxuriantly when inoculated intraperitoneally in R III mice. If transplanted to subcutaneous sites in the heterozygous MRC/H strain, the sarcoma often undergoes regression after considerable development. With a view to genetic selection and purification of the MRC/H strain and study of the regression phenomenon it seemed desirable to establish frozen stocks of the R III sarcoma.

It has of course long been known that tumours will survive in the frozen state. Ehrlich discovered this, but no serious attempt at practical application was made until Breedis and Furth (1938) investigated the matter. These authors demonstrated that various tumours could be preserved in the frozen state on CO_2 ice (−79° C.), for periods up to 400 days. There is an extensive but scattered literature relating to the survival of unicellular and other primitive organisms and also of some mammalian cells on freezing and thawing. The subject, up to 1938, has been reviewed by Luyet and Gehenio (1938). Of more recent work, I would select for special mention the convincing work of Briggs and Jund (1944), who showed by transposed transplanting of dorsal and ventral autoplastic grafts that normal mouse skin will survive sufficiently for grafting purposes when frozen for 1 hour to 24 hours at −78° C. Webster (1944), reporting results with refrigerated human skin grafts, describes takes with grafts refrigerated to −72° C. and with a lyophilized graft—i.e., one dried from the frozen state *in vacuo*.

Nearly all the reported observations on tumour survival in the frozen state relate to portions of tumour preserved *en masse*. One might expect that separated tumour cells exposed to an artificial fluid environment are more likely to be killed by freezing than cells situated in the interior of an intact portion of tumour. This, in fact, was the finding of Mider and Morton (1939). It will be remembered that the first specification I have outlined was as follows: "The preparations of tumour cells used for inoculation must be sufficiently homogeneous to obviate significant variations in the number of viable cells in different samples of a given volume of any given dilution." Obviously, homogenization of tumour preparations must be carried out before distribution to ampoules and preservation by freezing

From the theoretical point of view the possibilities are not encouraging if we consider the probable fate of cells suspended in any of the physiological salt solutions. When a salt solution freezes, ice crystals separate and the concentration of salt in solution increases until the eutectic concentration is reached. This eutectic concentration does not freeze unless the temperature is reduced to a critical level. Consider the figures for the salts present in Ringer's solution: the eutectic mixture of KCl with water is 25% and its freezing-point is −10.7° C.; of NaCl, 30.4%, with a freezing-point of −21.2° C.; of $CaCl_2$, 48%, with a freezing point of −52° C. This means, for example, that if a cell suspension is frozen at a temperature above −20° C. in 34 volumes of 0.85% NaCl, the volume of concentrated salt solution formed will be approximately equal to that of the cells, and its concentration will be 30%. Freezing under such conditions is therefore equivalent to soaking the cells in strong brine.

Preparation of Tumour Suspensions

Preliminary tests carried out with the R III and C3H sarcomas showed that when the tumour mince was diluted with more than a few parts of saline or Ringer's solution marked inactivation occurred on freezing and thawing. Other tests in which C3H sarcoma cells were held at 0° C. in various concentrations of NaCl or held in isotonic concentration for several hours at temperatures above and below −21° C. (the eutectic temperature of NaCl) showed that the rate and degree of inactivation were undesirably high. It seemed reasonable, therefore, to investigate the effect of substituting a non-electrolyte. Comparative tests with dextrose and saline solutions showed that sarcoma suspensions frozen in the former were much more active on thawing than suspensions prepared in the latter from the same lots of tumour mince. The optimum concentration of dextrose appeared to lie between 5 and 10%, but its protective effect was evident at from 3 to 40% if the suspensions were frozen without delay.

At this stage it became apparent that a better method of preparing tumour suspensions was required. A satisfactory solution, in the form of a pressure mincer, has been described (Craigie, 1949a). The later models of this instrument have been made entirely of stainless steel. Each mincer is provided with a set of four sliding-fit plungers provided with uniform longitudinal grooves. The groove sizes are 0.5, 0.25, 0.125, and 0.0625 mm. According to the consistency of the tumour and degree of mincing required, one or two plungers are selected and loaded in the barrel after the tumour tissue has been inserted. A portion of the suspending fluid is placed above the plunger. The plunger is then forced down by means of the screw, and the tissue passes through the plunger grooves into the suspending fluid.

To return to the problems of preserving tumour suspensions in the frozen state, I might mention that Breedis (1942) found that mouse leukaemic cells are inactivated if frozen too quickly in the temperature range of 0 to −15° C. A similar effect could not be demonstrated with the C3H sarcoma. This failure led to attempts to depress the freezing-point of suspensions in dextrose, one of which resulted in a striking demonstration of the survival of the C3H sarcoma under unexpected conditions. This has been reported (Craigie, 1949b), but the essentials are worth quoting.

C3H sarcoma mince was diluted to 1 in 12.5 (*a*) in 10% dextrose and (*b*) in 10% dextrose and 40% glycerol in water. Each suspension was distributed to several ampoules, sealed, frozen, and placed on CO_2 ice. The first test was carried out after the suspensions had been frozen for four days. Immediately after thawing, a portion of each was diluted with nine volumes of Ringer's solution. These dilutions, as well as the 1-in-12.5 concentrations, were injected subcutaneously in 0.1-ml. volumes, with the results shown in Table I.

TABLE I.—*C3H Sarcoma Suspension Frozen in Dilution of 1 in 12.5. 0.1 ml. Injected Subcutaneously after Thawing and Further Dilution*

Diluent	Time Frozen (Days)	Dilution Tested	No. of Tumours	Mean PMG (Days)
10% dextrose	4	1 : 12·5	6/6	8·0
	4	1 : 125	5/6	9·8
	253	1 : 17·5	12/12	4·17
	253	1 : 70	12/12	8·73
10% dextrose with 40% glycerol	4	1 : 12·5	6/6	11·0
	4	1 : 125	5/6	13·6
	253	1 : 17·5	12/12	4·08
	253	1 : 70	12/12	7·08

PMG = Period of microscopic growth, i.e., between inoculation and first appearance of tumour.

The preparation containing glycerol and dextrose appeared to be less active than the control. However, this may have been due to imperfectly developed technique and the use of Ringer's solution as a diluting fluid. A further test was undertaken after the preparations had been kept frozen for 253 days (Table I). In this test the dilutions were prepared in a saline–phosphate–cysteine mixture. As pointed out in the previous commentary on this experiment (Craigie, 1949b) the results, interpreted as being due entirely to the survival of tumour cells, indicate that at least 25% of the cells viable in the tumour mince before treatment survived dilution with 10% dextrose and 40% glycerol, freezing, preservation in the frozen state for 253 days, and subsequent thawing. In the light of more adequate data on the activity of freshly prepared C3H sarcoma-cell suspensions, this estimate seems to be confirmed. It is interesting to note that Polge, Smith, and Parkes (1949) have recently reported that glycerol protects spermatozoa against low temperatures. Fowl semen diluted with Ringer's solution showed no significant survival of spermatozoa after vitrification at −79° C. for 20 minutes and rapid thawing. On the other hand, the addition of 40% glycerol before freezing resulted in the resumption of full motility after thawing.

Effect of Dehydration

The preliminary results of the experiment with C3H sarcoma in dextrose and glycerol that I have quoted led to the adoption of drying techniques as a possible aid to the study of tumour survival on freezing, for the question of the role of dehydration by the suspending fluid inevitably arose. If dehydration were a factor, progressive loss of intracellular water at the low temperature of storage might be important. A few tests were carried out in which suspensions frozen in saline and in 5% dextrose were exposed to dehydrating agents *in vacuo* at −79° C. As expected, dehydration was extremely slow and further investigations were transferred from the CO_2 ice-box to the laboratory bench. It was planned to compare the effect of dehydration of tumour suspensions held in the frozen state at temperatures chosen in relation to the eutectic temperatures of Ringer's salts.

It might be noted that among the side-issues encountered during the development of equipment was the appearance of crystalline water-soluble and other organic substances in the water condensate. Back diffusion of pump oil was excluded, and the explanation seems to be that significant amounts of dried material from necrotic portions of tumour

were carried across in a microscopic state of division on the rapid current of water vapour. Tests of dried material obtained at various times during the development of the drying equipment (Craigie, 1949c) were negative, although one positive result was obtained later with C3H sarcoma and others were obtained by Gye, Begg, Mann, and Craigie (1949). On mature consideration of the problems involved it was decided to return to a study of the conditions of survival of activity of tumour suspensions on freezing, because freezing is the first step in freeze-drying. The need for quantitative methods also appeared to be urgent.

Degree of Survival

It had been found that a number of transplantable sarcomas and carcinomas could be preserved as suspensions in dextrose in the frozen state (Craigie, 1949b). In order to find out if primary chemically induced tumours would survive this treatment, groups of C3H mice of different ages were injected subcutaneously with 0.1% benzpyrene in arachis oil. A series of 19 tumours were removed at intervals ranging between 90 and 163 days from the injection and frozen in 5% dextrose in dilutions of 1 in 5 to 1 in 10. These were tested after being kept frozen for periods ranging from 36 to 96 days, and tumours were obtained in 17 of the preserved lots. (One other lot, diluted to 1 in 50 before freezing, failed to survive.)

It is evident from the results of this experiment that the degree of survival of the different tumours varied considerably. Some lots produced tumours at all sites injected, others at only some. The intervals elapsing between injection and appearance of the tumours ranged from 10 to 58 days. This variability in ability to survive freezing was also apparent in records of observations of other tumours. Although sporadic mammary carcinomas survive reasonably well, the best and most consistent survival has been obtained with tumours with a long history of transplantation. Sarcomas seem to be more resistant than carcinomas. Complete failure to survive freezing has been observed so far only with the two benzpyrene tumours mentioned and an undifferentiated tumour derived by Dr. Foulds from a squamous mammary tumour arising near the point of needle entry of intraperitoneal injection of methylcholanthrene.

From data which I shall present later it will be apparent that comparisons of activities of treated tumour preparations on the basis of percentages of tumours induced are of very doubtful validity. It cannot be too strongly emphasized that when suspensions of the C3H sarcoma are reduced by dilution or other means to a level of activity at which tumours fail to develop in 25% or more of the sites inoculated with a 0.1-ml. dose, the estimated order of survival is not more than one cell out of 100,000 or more cells viable in 0.1 ml. of the source tumour. The fallacy of comparing results on the basis of percentage of tumours obtained was not appreciated at first. In fact, until a year ago, attempts to obtain quantitative data on the survival of C3H sarcoma cells in various environments were based on the injection of a series of secondary dilutions with the object of identifying that giving 50% tumours. By way of excuse I might mention that titrations permitting observation or estimation of the 50% end-point are an integral part of modern and statistically acceptable methods used in exact work with pathogenic bacteria, viruses, and substances having an immunological or pharmacological action.

Fortunately, instead of recording the presence and size of tumours at weekly intervals, as is often practised with transplantable tumours, all mice were inspected daily and adequate records were available for analysis from experiments in which two to four dilutions or preparations were compared, not in different animals but at different sites in each member of a group. This is what emerged from an earlier experiment carried out with C3H sarcoma frozen in a dilution of 1 in 2.5 in (*a*) 5% dextrose and (*b*) 5% dextrose with M/150 phosphate buffer for four days. On thawing, dilutions were made in Ringer's solution to which 0.1% cysteine hydrochloride neutralized with phosphate had been added. Starting with the highest dilutions, two dilutions of each preparation were injected subcutaneously in 0.1-ml volumes in four groups of mice. The injections were deposited in the centres of the four abdominal quadrants; thus four comparisons were made in each mouse. When on later analysis the log of the dilution injected was plotted against the mean interval in days which elapsed before the tumour first became visible the picture shown in Fig. 1 was obtained.

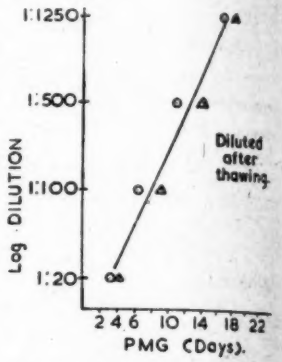


FIG. 1.—C3H sarcoma frozen with 1.5 parts of 5% dextrose (circles) and 5% dextrose and M/150 phosphate buffer (triangles).

This semi-logarithmic relationship suggests that any mean lag period* which may have intervened between inoculation and resumption of cell growth and mitosis was constant for all dilutions in this experiment and that the interval elapsing before the tumours became visible was primarily dependent on the volume of viable cells inoculated and the constancy of the average period between successive mitoses. There is reasonable agreement with the formulae:

$$T = L + \frac{m}{\log 2} \cdot \log \frac{1}{C},$$

$$\text{and } T_2 - T_1 = \frac{m}{\log 2} \cdot \log \frac{C_1}{C_2},$$

where T is the observed PMG value*; L, the lag period. m, the mean interval between successive mitoses; and C the concentration of viable tumour cells inoculated.

Of course, these formulae must not be taken too seriously at present. Things are not as simple as they might suggest, but it is of interest that sometimes they fit experimental results with astonishing accuracy for dilutions ranging from 1 in 50 to 1 in 1,000, and, further, that the value of "m," the mean interval between successive mitoses estimated from pairs of dilutions, has shown a remarkable constancy with unfrozen preparations. The formulae have proved useful in the analysis of experimental data because any statistically significant departures indicate that the simple, almost naive, assumptions involved are invalid on these occasions or that other factors, neglected in the formulae, have operated to a significant extent.

For example, tests checked with these formulae confirmed earlier suspicions about the inadequacy of Ringer's solution as a suspending fluid for tumour cells. However, before proceeding to discuss this, let me mention two rather striking and puzzling features about the development of tumours obtained with tumour-cell suspensions.

*The term "lag period" has been used in a different sense (Craigie, 1949b). Since lag period must be redefined as above, the abbreviation PMG (period of microscopic growth) is suggested to denote the time interval between the end of the lag period and the appearance of visible growth.

Rate of Growth

In the mouse a subcutaneous injection of 0.1 ml. spreads to occupy a visible area more than 1 cm. in diameter. It might therefore be expected that several discrete tumours would appear when multiples of the minimal tumour-inducing dose are given. This is rarely so. In fact, the only striking development of multiple tumours that has been encountered occurred with suspensions frozen with glycerol and dextrose. The second point is this: after a tumour has made its first appearance its growth rate is far from constant. The daily increments in diameter are quite erratic; after remaining practically stationary for several days a definite increase may occur within 24 hours. Following subcutaneous injection of a suspension of a rapidly growing sarcoma, tumours make their first appearance (*a*) as a somewhat irregular subcutaneous mass, or (*b*) as a nodule in the deeper layers of the dermis, or (*c*) as a muscle plaque. When first recognized the tumours are nearly always 1 to 2 mm. in diameter, or larger. They may appear within six hours. Thus there is at first sight a somewhat puzzling inconsistency between the sudden appearance of tumours and their frequent apparent quiescence for several days after they appear. Further, any attempt to base quantitative estimates on recorded dates of first appearance might seem to be a very questionable proceeding.

However, it must be borne in mind that if these tumours grew at a uniform rate around the time of the first appearance it would be very difficult to be certain on which day they first appeared. Actually there is no difficulty in ascertaining the date of first appearance. (I should add that a very small percentage disappear in 24 or 48 hours, in which event the record is cancelled.) It is evident that a detailed histological investigation of inoculated sites will have to be undertaken. However, adequate trial has shown empirically that data based on the times of first appearance of tumours induced by the inoculation of cell suspensions into 16 sites or more are much more likely to serve as a useful basis for quantitative comparisons than observations which record only the percentages of tumours obtained.

When it was found that dextrose was of value for preserving tumours in the frozen state, tests were undertaken to determine whether it was a desirable fluid for preparing dilutions of fresh or frozen and thawed suspensions for inoculation. It appeared to be somewhat inferior to salt solutions. Further observations were made from time to time, and the results can be summarized briefly. If dilutions are injected immediately they are prepared, physiological saline, saline with phosphate buffer, with or without cysteine, and Ringer's solution are definitely better than 5% dextrose. If there is a delay before injection of frozen and thawed preparations activity is reduced in all these solutions and the higher the dilution the greater the rate of inactivation. The need for a more satisfactory diluting fluid was emphasized by the tantalizing glimpses of tumour cells conforming to the simple and rational quantitative law suggested in Fig. 1. A further retreat was indicated and, in conformity with the principle that first things should come first, attention was concentrated on the survival of fresh unfrozen sarcoma cells.

When a C3H sarcoma is minced and series of dilutions from 1 in 50 to 1 in 1,000 are prepared in Ringer's solution and inoculated immediately, results illustrated by those shown in Fig. 2 are obtained. As in Fig. 1, a semi-logarithmic relationship between dose and mean time of appearance (PMG) of the tumours is strongly suggested. The curves on the left and right of Fig. 2 were obtained with healthy and necrotic tissue from the same tumour. The apparent discrepancy between these curves may be entirely referable to a less adequate dispersion of viable cells from the firmer healthy tissue, since the titration was carried out 10 months ago, using an earlier and less efficient model of pressure mincer. Another point to be noted is that the slope of the lines may be interpreted as a function of the mean interval between successive mitoses. If this is correct it may be calculated that 0.1 ml. of a 1-in-1,000,000 dilution of C3H sarcoma would produce tumours around

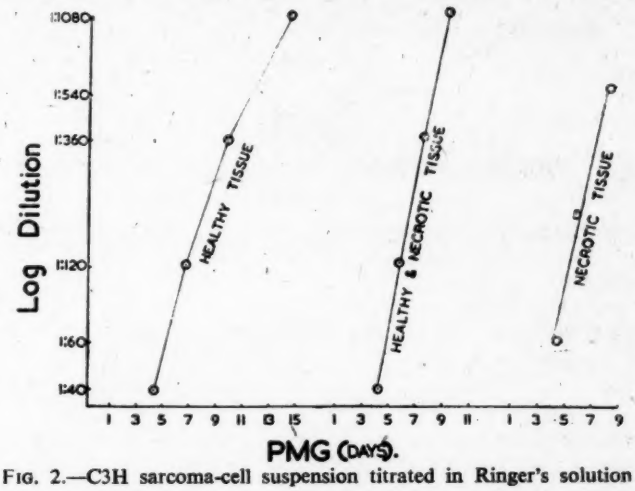


FIG. 2.—C3H sarcoma-cell suspension titrated in Ringer's solution

21 days after inoculation, provided that the cells remain viable in such high dilutions and the majority of single cells are capable of initiating tumours. However, this expectation cannot be realized.

Beyond a dilution of 1 in 1,000 there is a marked departure from the reasonably consistent relationship of log dose and mean PMG value observed with stronger concentrations. As the dilution is increased the percentage of tumours obtained falls off rapidly and their appearance is delayed. There are two possible interpretations. The minimal number of local concentrations of viable cells required to initiate a tumour in 75% of instances may be very large. Alternatively, Ringer's solution may exert a toxic effect when some unknown protective substance derived from the tumour tissue is diluted beyond an effective concentration.

A Different Approach

Attempts to increase the activity and stability of dilutions beyond 1 in 1,000 by the addition of tumour or muscle extracts or homologous blood and serum were unsuccessful. After reviewing the composition and history of the physiological salt solutions and fluids used to promote the survival of specialized cells it was decided to try a different approach. The differential balance of cations and anions across the limiting membrane of the living cell is such a fundamental fact that it is generally assumed that it must be maintained within reasonable limits if the cell is to survive. However, we must not confuse "survival" with maintenance of metabolic and functional activity. Suppose we could match the inorganic substances present inside the cell, ion for ion, across the cell membrane, would the effects be worth observing? Unfortunately, no complete figures for the composition of the intracellular fluid of tumour cells is available. The average figures for muscle tissue given by Muntwyler and Mautz (1947) have had to be used as a guide.

A preliminary investigation has been made of the survival of C3H sarcoma in fluids containing Na, K, Mg, and P in the same amounts as given in Fig. 3 for the intracellular

phase of muscle. These fluids are isotonic and adjusted to *p*H 7.3. It is hardly necessary to point out that precipitation of magnesium phosphate must be avoided in preparing them. There are obviously many organic substances which might be used to adjust the base balance, but trial has been limited to fluids containing lactate or succinate ions. In some tests the amount of organic anion has been reduced by the inclusion of carbonate, but this creates

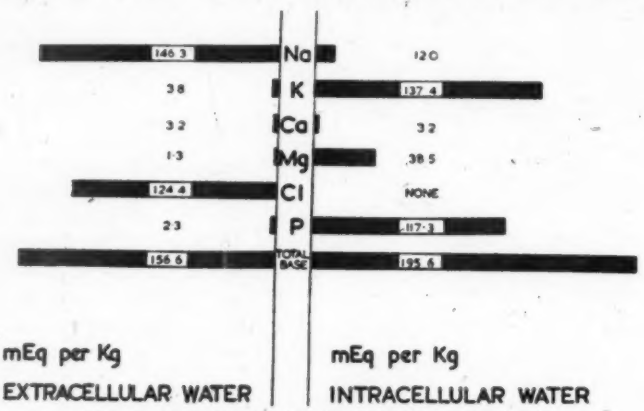


FIG. 3.—Ion distribution in skeletal muscle (dog).

difficulties in maintaining a constant *p*H. The succinate system has yielded more striking results than the lactate system.

Before quoting some experimental results I would like to mention two interesting points about the stability of these fluids. If the succinate system is heated to 48° C. it becomes turbid, and at higher temperatures a precipitate forms. If it is frozen and then thawed quickly it remains clear, but if it is thawed slowly a precipitate is obtained. However, precipitation on slow thawing is prevented if 2.5% or more of dextrose is added before freezing. The limited range of stability of this fluid is referable to the low solubility of magnesium phosphate and the solubility products of the various possible combinations of cations and anions in the mixture. The properties of this fluid, which is intended to resemble intracellular fluid in respect of balance of inorganic ions, invite speculation on the primary mechanisms of cell death on freezing and thawing and on exposure to the minimal lethal temperature.

Artificial Intracellular Fluid

Fig. 4 shows the results of a comparison of the survivals of C3H sarcoma cells in Ringer's solution and artificial intracellular fluid (A.I.C.F.) with succinate. A 1-in-5 suspension of sarcoma cells was prepared in 5% dextrose. This was diluted 1 in 10 and 1 in 50 (i.e., to 1 in 50 and 1 in 250) in (*a*) Ringer's solution and (*b*) A.I.C.F. The diluted suspensions were distributed to ampoules, which were sealed and kept in ice-water. Tests were carried out at two hours and after three, six, and eight days at 0° C. On each occasion each of the suspensions, in 0.1-ml. volumes, was injected subcutaneously in 16 mice. Four ventral sites were used in each mouse, one for each preparation, and the positions of the preparations were rotated to cancel out site variations. The date of first appearance of each tumour obtained is shown in Fig. 4.

The greater degree of survival in the succinate A.I.C.F. is obvious. It is also evident that the survival in the 1-in-250 dilutions is much shorter than that obtained with the 1-in-50 dilutions. It should be noted that both the Ringer and A.I.C F suspensions contained 0.5% dextrose carried over from the primary suspension.

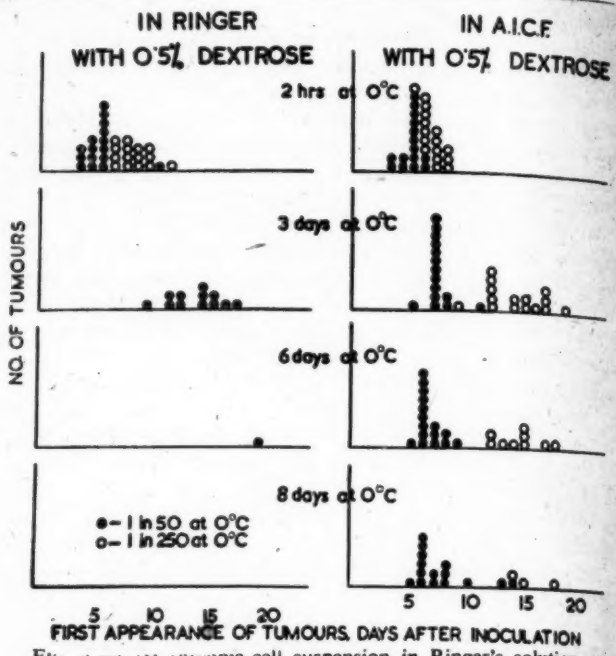


FIG. 4.—C3H sarcoma-cell suspension in Ringer's solution and A.I.C.F.

The superiority of succinate A.I.C.F. as a preserving fluid for sarcoma cells at 0° C. over Ringer's and Tyrode's solutions has been confirmed in a number of experiments. Significant survival up to 15 days has been observed.

TABLE II.—*C3H Sarcoma Cell Suspension Held in Succinate A.I.C.F. at 0° C. in a Dilution of 1 in 63*

Time Held at 0° C. Before Inoculation	No. of Sites Injected	Total No. of Tumours	Date of First Appearance of Tumours (Days After Inoculation)									
			2	3	4	5	6	7	8	9	10	11
3 days	12	12	0	0	9	1	1	0	0	0	0	1
9 ,,	16	16	0	0	4	8	3	1	0	0	0	0
15 ,,	16	16	0	0	0	3	9	3	1	0	0	0

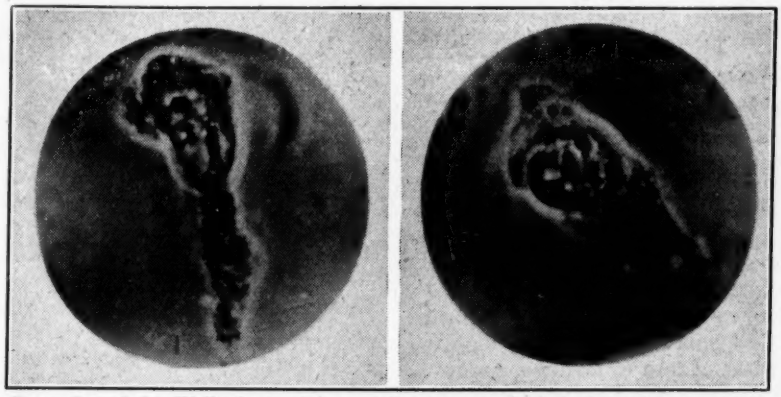
The results shown in Table II are taken from an experiment carried out to obtain data on the influence of Na and Mg ions. Only the results obtained with Na, K, and Mg in the proportions shown in Fig. 3 are shown. A considerable degree of survival (20 to 25%) occurred up to 15 days at 0° C. In this experiment no evidence that Na is essential to survival was obtained, but in the absence of Mg deterioration was rapid.

As a working hypothesis it might be assumed for the present that survival in A.I.C.F. is referable to abolition of the normal ion differential across the cell membrane and consequent depression of certain phases of cell metabolism. It might therefore be suggested that comparative studies of the survival of tumour cells in fluids of this type, in which the concentration of the inorganic ions and the nature of the supplementary organic base are varied, might provide an indirect approach to some cytochemical problems. Before leaving the subject of A.I.C.F. I might remark that if one wished to transmit an extremely labile virus from one cell to another it would be reasonable to guard it from the shocks of change in ionic environment. Some difficult mammalian viruses might be easier to handle in fluid which approximates in inorganic ion balance to the fluid in which they multiply within the cell.

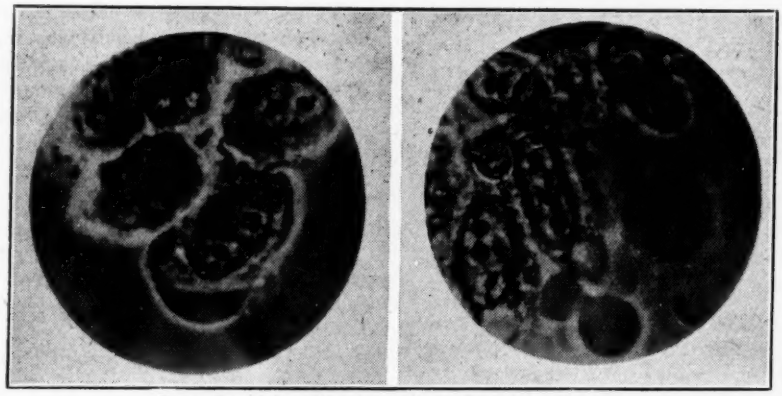
Nuclear and Cytoplasmic Changes

There is one further topic to which reference must be made—namely, the nuclear and cytoplasmic changes

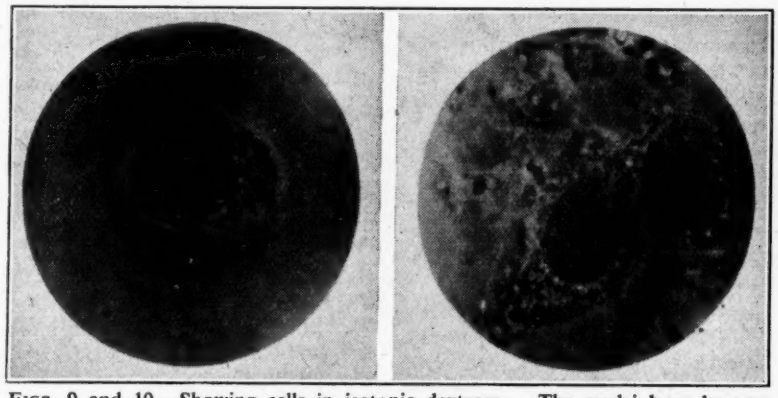
induced in tumour cells by the treatments I have mentioned. It has become essential to have an adequate record of the appearance of the cells in all suspensions tested by mouse inoculation. The routine which has been recently adopted is as follows. A portion of the suspension remaining in the syringe after injections are given is transferred to a cytometer slide. A number of fields are systematically recorded at a low magnification on fine-grain 35-mm. film of fixed contrast (Micro-Neg, Ilford) using phase contrast illumination. The phase-contrast photomicrographs of C3H sarcoma cells here shown will, I hope, make it obvious that detailed cytological studies are required in order to establish criteria of cell death under various conditions. As will be seen, nuclear and cytoplasmic detail is profoundly influenced by the fluid in which the cells are suspended. The photomicrographs were obtained from freshly prepared suspensions made from the same lot of C3H sarcoma mince. The photographic processing was strictly standardized, so that differences in contrast are comparable.



FIGS. 5 and 6.—Well-advanced intermediate stage which is immediately evident when C3H sarcoma cells are suspended in A.I.C.F.



FIGS. 7 and 8.—Showing cells in Tyrode's solution.



FIGS. 9 and 10.—Showing cells in isotonic dextrose. The nuclei have become swollen and are hyaline and vitreous in appearance.

Zollinger (1948) states that the brilliant type of nucleus, with bright nucleoli and double-contoured nuclear membrane, is a reliable sign of cell death, but there are grounds for doubt. When C3H sarcoma cells are suspended in A.I.C.F. a well-advanced intermediate stage is immediately evident (Figs. 5 and 6). Potocytosis (blistering proceeding to liberation of spherules of cytoplasmic fluid) seems to be a normal reaction of these cells to saline, Ringer's and Tyrode's solutions (Figs. 7 and 8, cells in Tyrode's solution), but it is very rarely seen in isotonic A.I.C.F. The effect of dextrose—a rapid disappearance of nucleoli and associated chromatin—has been described briefly (Craigie, 1949b). The nuclei, within a few seconds of contact of the cell with isotonic dextrose, become swollen and are hyaline and vitreous in appearance (Figs. 9 and 10).

Conclusion

In concluding this lecture I would like to emphasize that no certain evidence of the existence of a virus or transmissible agent, other than the Bittner agent, associated with transplantable mouse tumours is likely to emerge in the absence of adequate quantitative knowledge concerning the biomechanics of tumour-cell transplantation and the ability of the cells to survive under various conditions. The initial rather vague belief with which this work started has crystallized into the conviction I have expressed. There is a great deal that we do not know about the response of tumour cells to various artificial environments and the conditions necessary for their survival. There are some odd things about the way in which tumours appear after inoculation of tumour-cell suspensions that suggest the desirability of detailed histological examination of the inoculated sites. I, for one, when examining unfixed and unstained tumour cells under the phase microscope am often uncertain whether they are alive or dead. These problems may be approached in various ways, but they should, I think, be studied together and every endeavour made to place the observations on a quantitative basis so far as the materials permit.

REFERENCES

Bauer, D. J. (1949). *Nature*, **164**, 767.
Breedis, C. (1942). *J. exp. Med.*, **76**, 221.
—— and Furth, J. (1938). *Science*, **88**, 531.
Briggs, R., and Jund, L. (1944). *Anat. Rec.*, **89**, 75.
Craigie, J. (1949a). *Brit. J. Cancer*, **3**, 249.
—— (1949b). Ibid., **3**, 268.
—— (1949c). Ibid., **3**, 250.
Gye, W. E., Begg, A. M., Mann, I., and Craigie, J. (1949). Ibid., **3**, 259.
Ludford, R. J., and Barlow, H. (1945). *Cancer Res.*, **5**, 257.
Luyet, B. J., and Gehenio, P. M. (1938). *Biodynamica*, **33**, 1.
Mider, G. B., and Morton, J. J. (1939). *Amer. J. Cancer*, **35**, 502.
Muntwyler, E., and Mautz, F. R. (1947). In *Medical Physics*. edited by O. Glasser, 1944. Reprinted 1947. Year Book Publishers Inc., Chicago.
Polge, G., Smith, A. U., and Parkes, A. S. (1949). *Nature*, **164**, 666.
Webster, J. P. (1944). *Ann. Surg.*, **120**, 431.
Zollinger, H. U. (1948). *Amer. J. Path.*, **24**, 1039.

ANTICOAGULANT THERAPY*

BY

H. W. FULLERTON, M.A., M.D., F.R.C.P.

AND

G. ANASTASOPOULOS, M.D.Athens

(From the Department of Medicine, University of Aberdeen)

There is little disagreement about the value of heparin in the prophylaxis and treatment of thrombosis, and considerable quantities of this expensive drug are now used. The control of the dosage, however, often seems to be unsatisfactory, and we feel that more would be gained by giving larger and fully effective doses to a smaller number of carefully selected cases. The aim should be to maintain the clotting time at about 30 minutes instead of the normal 6–10 minutes, and this seems seldom to be achieved by the usual practice of intravenous injections of 50–75 mg. four-hourly. It is probably more efficacious to give a continuous intravenous drip of heparin in saline (say 100 mg. per pint, or 175 mg. per litre) at a rate of 15 to 25 drops a minute, the rate being adjusted at intervals so as to maintain the desired prolongation of coagulation. But until we have available effective preparations of heparin with an action lasting many hours when given intramuscularly it is unlikely that this drug will be employed for more than a few days at a time, and in the great majority of cases of thrombosis effective treatment for much longer than this is desired.

Dicoumarol

This brings us to consider dicoumarol, which is given orally and is thought to prevent the development or extension of thrombosis by lowering the prothrombin and thereby the coagulability of blood and we propose to confine the rest of the paper to a consideration of this drug, which is now widely used in the treatment of many forms of venous and arterial thrombosis.

Dicoumarol has not proved to be one of those drugs which fade into disuse after a short period of popularity. Rather the reverse is true, and as time has passed and more and more reports have appeared its place in the treatment of thrombosis has become more firmly established. It is true, of course, that many of these reports have dealt with such small numbers of cases that their value has been negligible, but several large and well-controlled series have been published, and these are impressive enough to justify its use. A committee of the American Heart Association has recently reported the results in 800 cases of coronary thrombosis (Wright *et al.*, 1948). Of these, 368 patients admitted on even days received conventional treatment without anticoagulants; and 432 admitted on odd days were given the same conventional treatment with the addition of anticoagulants, mainly dicoumarol. While the mortality rate in the control group was 24%, in the treated group it was 14.9%, and this reduction was accounted for mainly by the much smaller number of deaths after one or more thrombo-embolic complications in the treated group.

More than 25% of the control group developed one or more thrombo-embolic complications, as compared with about 12% in the treated group. Moreover, in only about 6% did these complications occur at a time when the anticoagulant therapy could reasonably be expected to be effective.

The incidence of the various thrombo-embolic complications was noted, and it was found that for extensions of the original infarct, for new infarctions, for pulmonary, cerebral, and peripheral emboli, and for venous thromboses the incidence was notably less in the treated group.

These results provide striking confirmation of the effectiveness of dicoumarol as an anticoagulant and are likely to increase its use in coronary thrombosis considerably. The results of its use in venous thrombosis are also striking, although frequently the findings have not been so well controlled.

Unfortunately two considerations have to be borne in mind before a decision to use it as a routine can be adopted. First, no uniform scheme of dosage can be prescribed, because of the marked individual variation in response. Secondly, dosage must be carefully controlled, because not infrequently a haemorrhagic tendency, which may be severe, complicates treatment. This is often due to too great lowering of the prothrombin level of the blood. Accordingly, dosage in each case must be controlled by regular estimations of plasma prothrombin—ideally every day, certainly not less often than every second day. In our opinion this consideration should limit the use of dicoumarol to patients in hospitals with adequate facilities for these tests. Even in these circumstances haemorrhage—e.g., severe haematuria—will occasionally occur. Without such careful control one of two things is likely to happen: either small ineffective doses will be used or effective doses will lead to some disastrous haemorrhages.

On the question of what test should be used to control the dosage there has been much difference of opinion and confusion of thought. It is now possible to clear away some of the misconceptions which have arisen in the past few years and therefore to understand better the significance of the different techniques of so-called "prothrombin estimation." Certainly the lack of knowledge concerning these techniques and the resulting confusion have prevented dicoumarol being used on a much wider scale.

The simplest theory of blood coagulation is that of Morawitz, who describes the process as occurring in two steps: (1) thrombokinase + prothrombin + calcium → thrombin; (2) thrombin + fibrinogen → fibrin. It used to be thought that thrombokinase was derived mainly from disintegrating platelets in shed blood and from tissue cells damaged in a wound; now its main source is believed by some to be a precursor in the plasma (Lozner *et al.*, 1942). According to this theory it converts prothrombin to thrombin in the presence of free calcium ions. When enough thrombin has accumulated the soluble protein fibrinogen is converted to strands of fibrin which contain the red cells and serum in their meshes.

Prothrombin Estimation

(*a*) *Quick's Method.*—This is based on the above theory, and is widely used in America and this country in the control of treatment with dicoumarol. In this method the source of thrombokinase is a suspension of acetone-dried rabbit brain. A similar substance can be obtained from most tissues—e.g., several workers have used an extract of lung, and now human brain is widely employed.

The essential steps in the test are: (1) 4.5 ml. of blood is mixed with 0.5 ml. of oxalate solution. The calcium is thereby removed and development of Stage 1 is prevented. (2) To 0.1 ml. of plasma the same volume of brain-powder suspension is added—the tube being held in a water bath at 37° C. (3) Then 0.1 ml. of calcium solution is added

*Read in the Section of Medicine at the Annual Meeting of the British Medical Association, Harrogate, 1949.

quickly and the time between this addition and the formation of fibrin is noted, a stopwatch being used.

This is the so-called "prothrombin time." The theoretical justification for regarding this time as an indication of the prothrombin content of the plasma is that when optimal amounts of thrombokinase and calcium are added the only variable in Stage 1 is the amount of prothrombin. Therefore the smaller the amount of prothrombin the longer the time before enough thrombin is formed to bring about Stage 2.

Various workers have found different times with Quick's method in normal plasmas, usually ranging between 15 and 30 seconds. This is because different batches of brain extract vary in potency, and the normal time for each batch must be carefully determined before the test is used in patients. Moreover, the preparation of the powder is tedious.

(*b*) *Russell Viper Venom.*—The foregoing considerations led one of us (H.W.F.) to suggest the use of Russell viper venom as the source of thrombokinase in this test (Fullerton, 1940). Six years earlier Macfarlane and Barnett (1934) had investigated the possibilities of this substance in their search for a local haemostatic effective in haemophilia. They found that the venom was capable of accelerating the clotting of haemophilic blood in dilutions of 1 in 10^{12} or more. It did not clot oxalated or citrated blood unless calcium was added, and it did not clot solutions of fibrinogen. Accordingly, its action was that of a powerful thrombokinase.

As a result of this work Russell viper venom was produced commercially. The best-known preparation is "stypven" (B.W. and Co.): 0.1 mg. of dried venom and 1 ml. of distilled water are supplied in separate ampoules and the solution is made shortly before use. Different batches differ little in potency, and with normal plasmas "prothrombin times" of 18–25 seconds are usually obtained; consequently the careful standardization of each batch is unnecessary. Apart from this difference in the source of thrombokinase the technique is the same as Quick's.

(*c*) *Venom plus Lecithin.*—The venom method was quickly followed by a third. Witts and Hobson (1940) described a series of observations in which they used a mixture of venom solution and ovo-lecithin as the thrombokinase. Normal plasmas gave very short "prothrombin times" of 6–10 seconds, so it is evident that some substance in the ovo-lecithin potentiates the action of the venom. Witts and Hobson, and recently Biggs and Macfarlane (1949), added an alcoholic solution of lecithin to the venom. With this method we have had variable results. We believe that it is much more satisfactory to use water instead of alcohol as the solvent. When ovo-lecithin is dissolved in water containing 0.5% phenol the solution retains its full activity for several months. This solution is added to a freshly opened ampoule of venom in the usual proportion (1 ml. to 0.1 mg. venom). With this modification the method is therefore a very simple one to use. With it we have not observed the marked day-to-day variations recorded by Biggs and Macfarlane during treatment with dicoumarol, nor have we found it insensitive as an indication of the effects of this drug; in fact, definite prolongation of the time has usually been observed on the second or third day of treatment—i.e., at the same time as changes occur when brain powder is used.

The questions then arise: How do these three methods compare? Do they measure the same factor when they are used to control the dosage of dicoumarin, or is one to be preferred to the others when it is used in this way? These questions can be answered satisfactorily if we base our deductions on a theory of coagulation slightly different from that of Morawitz.

Role of the Lipoid Factor

There seems no doubt that a lipoid substance is essential for the coagulation of blood. For example, Macfarlane *et al.* (1941) have shown that oxalated plasma from which the fat has been removed by high-speed centrifuging or by extraction with carbon tetrachloride will not clot after the addition of a fat-free thrombokinase such as viper venom and calcium unless some lipoid material like ovo-lecithin or cream is added as well. We believe that it is not only essential in the first stage of coagulation but that it is a separate and distinct substance—in a way similar to calcium but with the difference that while it is simple to free a plasma of the calcium ions without disturbing the other factors concerned in coagulation it is very difficult to free it entirely of the lipoid substance. Moreover, alterations probably occur in the concentration of this lipoid factor in the plasma of a degree sufficient to alter the coagulability of blood.

If we accept this theory then the following is clear:

(1) That with the venom+lecithin method optimal amounts of thrombokinase and the lipoid activator are added in the test. Therefore this method measures the prothrombin level but will not reveal alterations in coagulability due to variations in the plasma level of the lipoid factor.

(2) Brain extract contains optimal amounts of lipoid factor and variable and suboptimal amounts of thrombokinase. The results of a representative experiment illustrate this point (Table I). All the estimations were made in one sample of plasma. With venom alone an average time of 22.5 seconds was obtained. With the particular batch of brain we were then using the time was 24.1 seconds; with venom+lecithin it was 9.3 seconds. Adding ovo-lecithin to the suspension of the brain powder produced no shortening of the time: this indicates that the brain extract already contained an optimal amount of the lipoid factor. But the addition of venom (0.1 mg. per ml.) to the brain suspension reduced the time to 10.8 seconds, which is not significantly longer than the result with venom+lecithin (9.3 seconds). This indicates that the concentration of thrombokinase in the brain suspension is suboptimal.

TABLE I.—*Prothrombin Time with the Various Methods*

Thrombokinase	"Prothrombin Time"
Venom	22·5 secs.
Brain powder	24·1 "
Venom + Lecithin	9·3 "
Brain powder + Lecithin	25·4 "
Brain powder + Venom	10·8 "
Brain powder + Venom + Lecithin	10·2 "

We believe, therefore, that Quick's test, like the venom+lecithin method, measures prothrombin but not changes in coagulability due to variations in the lipoid factor. Since optimal concentrations of thrombokinase and the lipoid factor can be assured with the venom+lecithin method it would seem preferable to the brain extract method.

(3) When venom alone is used we have a thrombokinase which is free of lipoid factor. Accordingly, by this method the so-called "prothrombin time"—the "accelerated clotting time" is a better term—is an accurate measure of prothrombin only if the concentration of lipoid factor in the plasma is within the normal range. And, conversely, if the prothrombin is constant this test will measure variations in the lipoid factor in the plasma.

The justification for these statements and their practical importance is based on the following experimental work.

Effect of Alimentary Lipaemia

The effect of lipaemia on the coagulability of blood following a high-fat meal was determined by the "accelerated clotting time," venom being used as the thrombokinase.

When the ordinary ward meals are taken there is no significant variation in the accelerated clotting time throughout the day; this conclusion is based on a study of eight patients. But in a group of six patients given a breakfast containing 85 g. fat (bacon and eggs and bread-and-butter) the results were striking (Table II).

TABLE II

Case	Fasting	During Lipaemia	Difference	Time of Shortest Reading After Meals
	Fat Intake 85 g.			
1	24·5 sec.	10·9 sec.	13·6 sec.	5 hours
2	22·3 ,,	13·4 ,,	8·6 ,,	4¾ ,,
3	23·0 ,,	12·8 ,,	10·2 ,,	3 ,,
4	24·3 ,,	17·5 ,,	6·8 ,,	2½ ,,
5	22·3 ,,	14·8 ,,	8·0 ,,	3¼ ,,
6	24·7 ,,	13·1 ,,	11·6 ,,	3¼ ,,
Average ..	23·5 ,,	13·7 ,,	9·8 ,,	

In the second column is shown the accelerated clotting time in seconds with the patients fasting (average 23.5); in the third the shortest accelerated clotting time during the lipaemia (average 13.7 seconds); next the difference between the fasting and the shortest times (average 9.8 seconds); and lastly the time of the shortest reading in hours after the meal. In each patient a much shorter time was found at the height of the lipaemia.

Chart I shows the details in one case. The curve marked V represents the accelerated clotting times with venom as the thrombokinase falling from about 25 seconds fasting to 10.9 seconds at the height of the lipaemia. The line V+L was obtained by using venom and lecithin as the thrombokinase; it runs in a more or less horizontal line. The line R.B. was obtained by using rabbit brain extract; it too runs horizontally.

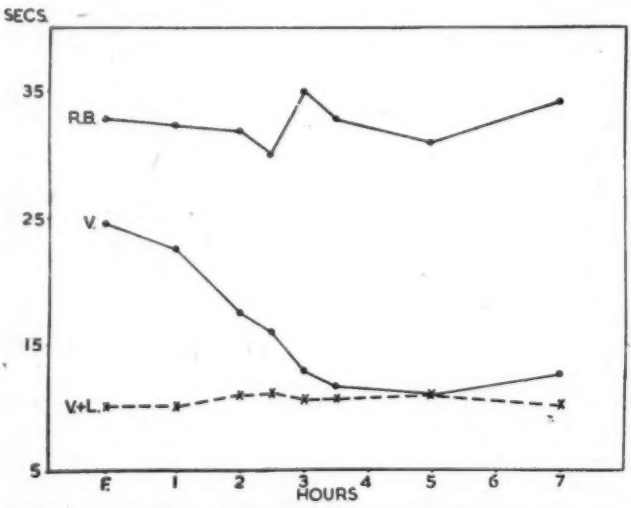


CHART I.—Accelerated clotting times in a patient after a meal containing 85 g. of fat.

Therefore we can conclude that accelerated clotting times determined by the use of venom show marked shortening during lipaemia, a result which is obscured by the use of venom+lecithin and of brain extract, because both these reagents contain an optimal amount of the lipoid factor essential for clotting.

Effect of Alimentary Lipaemia during Treatment with Dicoumarol

The next step was to investigate the effect of alimentary lipaemia in patients in whom dicoumarol treatment had produced a low prothrombin level. This was done in eight patients. The results varied according to the time after the start of dicoumarol treatment when the test was done and also according to the degree to which the prothrombin level had been depressed by the treatment. But it was very clear that the shortening of the accelerated clotting time produced by alimentary lipaemia was much less marked during dicoumarol treatment, and in some cases it was absent altogether.

One example will suffice (Chart II). The patient had received dicoumarol treatment for coronary thrombosis. The accelerated clotting time with venom with the patient fasting was 33.7 seconds. He then took the meal containing 85 g. fat, and at intervals of one hour, two hours, two and a half hours, three hours, and three and three-quarter hours thereafter the times were 32.9, 33.6, 32.6, 31.1, and 33.2 seconds: that is, there was no significant shortening after the meal. The venom+lecithin curve runs horizontally and the rabbit brain extract curve horizontally with some irregularity.

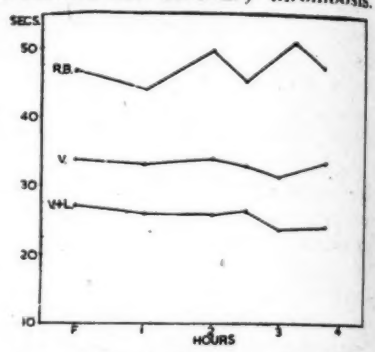


CHART II.—Accelerated clotting times in a patient undergoing dicoumarol treatment and after a meal containing 85 g. of fat.

We believe that the explanation for this striking difference is that when one component in the first stage of coagulation—viz., prothrombin—is depressed by dicoumarol a compensatory increase in another component—the lipoid factor—occurs and so lessens the reduction in coagulability produced by the drug. Alimentary lipaemia produces little or no shortening of the accelerated clotting time when the effects of dicoumarol are marked, because even in the fasting state the plasma level of the lipoid factor may be nearly optimal.

Further evidence in support of this theory is provided by comparing the results obtained by the use of the venom and the venom+lecithin tests throughout the period of dicoumarol treatment. Chart III illustrates the typical findings. Before treatment the accelerated clotting time with venom was 22 seconds; with venom+lecithin 10.5 seconds. Then 1,700 mg. dicoumarol was given over a period of seven days. Increases in the clotting times occurred with both methods, but the difference between the two became less, and it increased again as the effect of the dicoumarol passed off. We believe that this result is due to an increase in the lipoid activator in the plasma, which

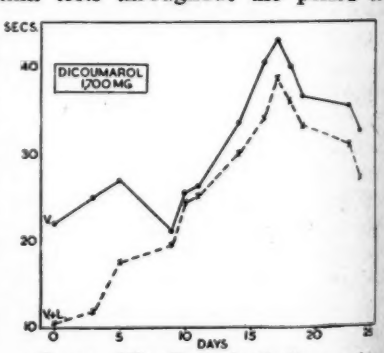


CHART III.—Typical findings when 1,700 mg. of dicoumarol was given for seven days.

after some time reaches nearly an optimal concentration. The effect of this is that the addition of lipoid factor to the venom—as in the venom + lecithin test—produces little or no potentiating action.

On the basis of these results it may be concluded that when dicoumarol is controlled by tests using venom + lecithin or brain extract a reasonably accurate assessment is obtained of the reduction in prothrombin produced by the treatment. But this reduction in prothrombin does not accurately represent the effect of dicoumarol on the coagulability of the blood, since an increase in lipoid factor follows the reduction in prothrombin. The test using venom alone reflects this alteration in coagulability, but does not accurately determine the reduction in prothrombin.

Effect of Haemolysis

One additional point of considerable practical importance is that slight haemolysis produces considerable shortening of the accelerated clotting time when the venom test is used, but not with the venom + lecithin and brain extract tests.

Chart IV illustrates this point. Haemolysed solutions were prepared by adding one volume of packed red cells

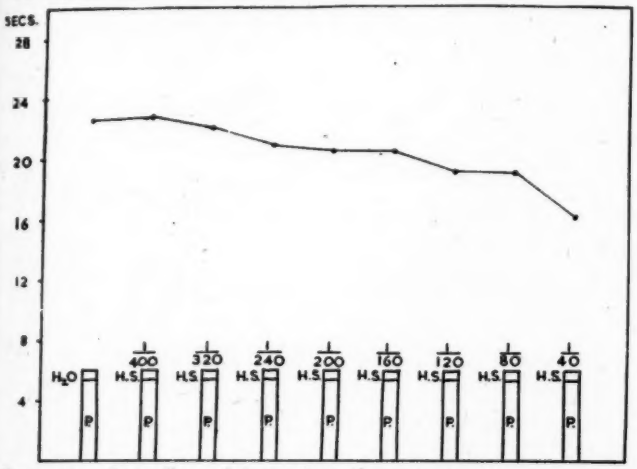


CHART IV.—The effect of haemolysis in shortening the accelerated clotting time with the venom test.

to different volumes of distilled water—one volume of cells in 400 of water, one in 320 of water, one in 240, and so on up to one in 40. One volume of the resulting solutions was then added to nine volumes of plasma, and as a control one volume of water was added to nine volumes of plasma. The accelerated clotting times using venom were then estimated in each, four determinations being made and the average taken. It is clearly seen that as the strength of the haemolysed solution increases the clotting time falls from the control level of 22.6 seconds to 16.1 seconds. We particularly wish to stress that in the range of haemolysed solutions used in this experiment the presence of haemolysis could be recognized macroscopically only at the right-hand end of the scale; in the last plasma slight but definite haemolysis was discernible; in the next a mere trace; in the next it was doubtful; and in the others haemolysis could not be detected.

It is clear, therefore, that when the venom test is used the greatest possible precautions must be taken to avoid haemolysis; the syringe must be dry and must be manipulated gently, and inversion of the tube to ensure mixing of blood and oxalate solution must be done very carefully.

Failure to appreciate the effect of haemolysis has been responsible for some of the confusing results reported. For example, recently there appeared an article by James (1949), who set out to compare the venom and the brain test in patients treated with dicoumarol. He used oxalate crystals instead of solution, and to ensure that they dissolved rapidly in the blood he shook each sample well. Obviously he was producing variable degrees of haemolysis, and accordingly his results with the venom test must be discounted.

The active agent in the red cells which produces this effect is probably the lipoid factor in the cell envelope; hence the effect is not seen with the venom + lecithin and brain extract tests.

Conclusion

Lastly the question arises, Which is the best test to use in the control of dicoumarol treatment? The answer is, I think, that it does not matter greatly which is used: the important points are to understand clearly the significance of the findings and to carry out the test with scrupulous attention to detail.

We use both the venom and the venom + lecithin method in each case. This entails very little extra work and the findings give important information. We aim to maintain the accelerated clotting times at about 25 seconds with the venom + lecithin test and at 35–40 seconds with the venom test—i.e., less prolongation proportionally with the latter. Prolongations of the time with the venom test require a larger dosage of dicoumarol and indicate a lower concentration of prothrombin than comparable prolongations with the venom + lecithin and brain tests. A failure to appreciate this point has caused much confusion and has been responsible for the view that the venom test is not suitable for the control of dicoumarol treatment. We do not express the results as a percentage of normal: this involves making unwarranted assumptions and confuses the picture. Until standard preparations of brain powder are obtainable we can see no theoretical advantage in using them. It would seem that their use is unlikely to give any more valuable information, but a careful comparison of the three tests has not yet been reported.

We give 300 mg. of dicoumarol on the first day and 200 mg. on each of the two succeeding days. Further treatment is not given until the effect of these initial doses is seen, and then the dosage depends not only on the degree of prolongation of the accelerated clotting time but also on the speed with which this develops. No definite rules can be given; each case must be considered individually, and some experience is necessary before the desired prolongation can be attained and maintained. On several occasions haematuria has developed: we have used no special treatment for it apart from stopping dicoumarol, and no harm has resulted.

Summary

The value of heparin and dicoumarol is briefly appraised, and the difficulties of calculating accurate dosage are mentioned. Three methods of determining blood coagulability are described. The role of the lipoid factor in blood clotting is discussed from this standpoint. An account is given of experimental work showing the effect on the coagulability of the blood of lipaemia and haemolysis, and important points of technique in tests of blood coagulability are emphasized.

REFERENCES

Biggs, R., and Macfarlane, R. G. (1949). *J. clin. Path.*, **2**, 33.
Fullerton, H. W. (1940). *Lancet*, **2**, 195.
James, G. A. (1949). *J. clin. Path.*, **2**, 45.
Lozner, E. L., Taylor, F. H. L., and Macdonald, H. (1942). *J. clin. Invest.*, **21**, 241.
Macfarlane, R. G., and Barnett, B. (1934). *Lancet*, **2**, 985.
—— *et al.* (1941). *J. Physiol.*, **99**, 7.
Quick, A. J. (1942). *The Haemorrhagic Diseases*, p. 312. Thomas, Springfield, Illinois.
Witts, L. J., and Hobson, F. C. G. (1940). *British Medical Journal*, **2**, 862.
Wright, I. S., Marple, C. D., and Beck, D. F. (1948). *Amer. Heart J.*, **36**, 801.

THE EXCRETION OF CHORIONIC GONADOTROPHIN BY PREGNANT DIABETICS

BY

J. A. LORAINE, M.B., Ch.B., Ph.D., M.R.C.P.Ed.

From the Medical Research Council's Clinical Endocrinology Research Unit, Edinburgh University

The quantitative estimation of chorionic gonadotrophin (C.G.) in the blood and urine of pregnant women has assumed new importance from the diagnostic point of view since the work of White (1937, 1943, 1946, 1947), White *et al.*, (1939), and White and Hunt (1943) on pregnancy complicated by diabetes and of Smith and Smith (1935, 1936, 1941, 1948), Watts and Adair (1943), and Smith, Smith, and Hurwitz (1944) on the toxaemias of pregnancy.

Although the introduction of insulin greatly reduced the maternal mortality rate in pregnant diabetics (Kramer, 1935; Lawrence and Oakley, 1942), the foetal mortality in such cases has not shown a corresponding decline (Herrick and Tillman, 1938; Gilbert and Dunlop, 1949; Barns and Morgans, 1949). It is evident that foetal wastage remains the great obstetrical problem in diabetes, and in some series of cases the foetal loss rate has been over 50%.

Set in this background, therefore, the great reduction in foetal mortality rate obtained by White (1946, 1947), using hormonal therapy in the form of oestrogens and progesterone in a proportion of these cases, is very striking indeed. Estimations were made by White of the serum chorionic gonadotrophin, using corpora lutea in immature female rats as the end-point of the biological assay: urinary pregnanediol was estimated by the Venning (1937) method and subsequently by that of Astwood and Jones (1941). A few assays of oestrogens in the serum were performed by biological methods.

From a study of 300 consecutive cases of pregnancy complicated by diabetes White (1947) found that such patients could be divided into two groups, each carrying an entirely different prognosis.

The first group consisted of 66 patients in whom the C.G. readings throughout pregnancy were classified as normal. In this group the foetal survival rate was 97%, the incidence of premature deliveries was 0, and that of pre-eclampsia 2%. The second group (over 75% of the 300 consecutive cases) was said to suffer from "hormonal imbalance" during pregnancy. The C.G. levels were abnormally high, and this finding was often associated with a low urinary pregnanediol and a low serum oestrogen. Of the patients in this group, 58 received no hormonal therapy and the foetal survival rate was only 47%; premature delivery occurred in 40% and pre-eclampsia in 50%. In addition many of these patients delivered babies which were grossly over weight.

Since this change in C.G. level preceded, often by some weeks, any obstetrical accident it was concluded that a rise in the serum C.G. could be regarded as the harbinger of an impending disaster. A group of 174 cases showing "hormonal imbalance" were treated with oestrogen and in most cases with progesterone as well. In these patients the foetal survival rate rose to 90%; premature delivery occurred in only 5%; pre-eclampsia in 5%, and the majority of patients receiving this treatment delivered babies of normal size.

A method of assay of C.G. depending on the increase in prostatic weight in immature rats and based on the use of the International Standard preparation of C.G. is described elsewhere (Loraine, 1949). This method was applied to the estimation of C.G. in the urine of normally pregnant women. In these normal cases very high readings, such as 25,000–30,000 i.u. of C.G. per 24 hours, were obtained from the 40th to the 80th day of pregnancy as calculated from the date of the last menstrual period. This was followed by a gradual decline, and from the 100th day until the end of pregnancy the excretion of C.G. was between 4,000 and 10,000 i.u. per 24 hours.

In Fig. 1 is shown the complete range of all the estimations made on the urines of normal pregnant women. The figures are quantitatively similar to those of Jones, Delfs and Stran (1944), who also used the International Standard but estimated C.G. in the serum. Curves of the same general shape have been obtained by other workers, who expressed their results in arbitrary "rat units" (Cole and Saunders, 1935; Browne and Venning, 1936; Smith and Smith, 1936; Boycott and Rowlands, 1938; Browne, Henry, and Venning, 1939; Siegler, 1939; Rakoff, 1939; Taylor and Scadron, 1939; Venning, 1948). Although the series of cases was a relatively small one, the variations in the amount of C.G excreted per 24 hours during the second and third trimesters of pregnancy were smaller than has been generally supposed, and much of the apparent variation shown by previous workers has probably been due to the use of relatively inaccurate assay methods.

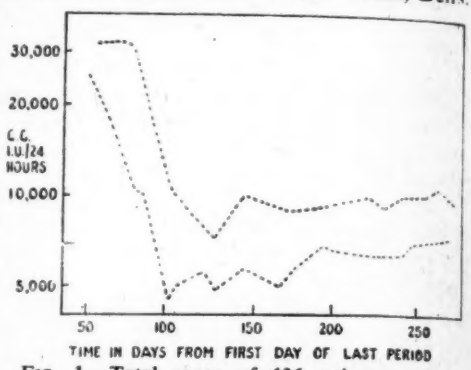


FIG. 1.—Total range of 136 estimates of the excretion of chorionic gonadotrophin in normal pregnancy.

The number of pregnant diabetics studied is as yet too small to assess adequately the effect of stilboestrol in reducing the foetal mortality rate. The present communication is concerned with the excretion of C.G. by diabetic women and the effect of oestrogens on this excretion in normal women and in diabetic women.

Methods.—The method used depends upon the increase in the prostatic weight in immature rats after subcutaneous administration of the urine to the animals. The results of the assay are always expressed in i.u. of C.G. per 24-hour specimen of urine. The technique is described in detail in the previous paper.

Results

The effect of orally administered stilboestrol on the C.G excretion in two normally pregnant women was investigated. Fourteen pregnant diabetics were considered in all, and 11 of these had C.G. estimations made at approximately weekly intervals after diagnosis. Only a few readings were made on the other three patients. Stilboestrol was administered to these diabetics, who after 100 days of gestation consistently showed an excretion of C.G. above the normal level of 10,000 i.u. per 24 hours. Six of the 14 cases were shown to have abnormally high C.G. readings at some stage of their pregnancy, and the findings in these cases are discussed below. In the other eight patients the excretion of C.G. appeared to be normal.

Normal Pregnancy

Case 1.—After two weeks' control period stilboestrol in dosage of 25 mg. a day was started at the 21st week of pregnancy (Fig. 2). The dose was increased to 30 mg. a day at

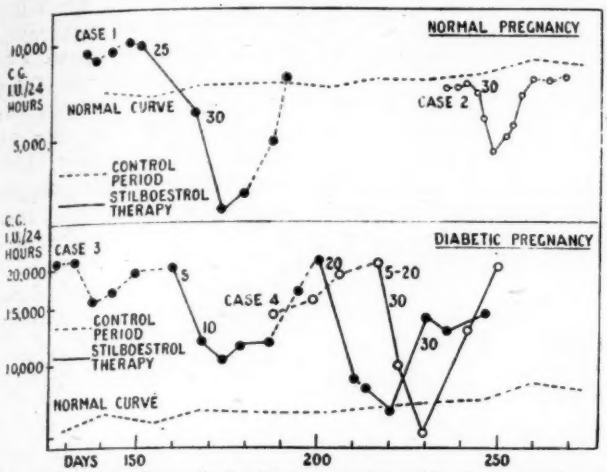


FIG. 2.—Excretion of chorionic gonadotrophin by normal and diabetic women treated with stilboestrol. The small figures denote doses (mg. per day) and are placed at the times these were started. (Cases 1–4).

the 23rd week. A sharp fall in the C.G. excretion occurred, the reading climbing back to just below its original level on cessation of the treatment.

Case 2.—After one week's control period stilboestrol in dosage of 30 mg. a day was given at the 34th week of pregnancy (Fig. 2). A modest depression of the C.G. level ensued initially, but when the same dose of stilboestrol was continued the excretion of the hormone returned to its original level, this occurring after approximately three weeks' therapy.

Pregnancy in Diabetics

Case 3.—Estimations made from the 17th to 23rd weeks of pregnancy showed an abnormally high excretion of C.G. (Fig. 2). Stilboestrol in relatively small dosage was started at the 23rd week and it produced a significant fall, but the reading rose to slightly above its original level on cessation of the therapy. Subsequent therapy with larger dosage started at the 28th week produced another dramatic fall in the C.G. excretion, but an "escape" phenomenon occurred when the same dosage was maintained. This patient was delivered at the 36th week by caesarean section. The weight of the baby was 6 lb. 7 oz. (2.92 kg.) and of the placenta 1 lb. 10 oz. (0.74 kg.).

Case 4.—An abnormally high C.G. excretion was found when the first estimations were made on this patient at the 27th week of pregnancy (Fig. 2). The dosage of stilboestrol started at the 31st week was rapidly increased by 5 mg. a day to 30 mg. a day and maintained at this level. A rapid initial fall in the C.G. excretion was observed, but this was followed by a rise to approximately the original level after four weeks' treatment. The patient was delivered vaginally at 36 weeks. The birth weight of the foetus was 4 lb. 11 oz. (2.13 kg.) and of the placenta 1 lb. 3 oz. (0.54 kg.).

Case 5.—The very high readings of C.G. obtained in early pregnancy in this patient were originally thought to indicate a delayed peak period, but the excretion remained consistently high well after the 100th day of pregnancy (Fig. 3). Stilboestrol in dosage of 25 mg. a day was started at the 15th week of pregnancy, and this was increased to 30 mg. a day at the 17th week. A fall in the excretion of C.G. occurred, but the titre rose again on cessation of the treatment. Therapy was restarted at the 20th week in dosage of 20 mg. a day, and this was increased to 30 mg. a day at the 25th week. This resulted in a fall in the urinary excretion of C.G. to 10,000 i.u. by the 27th week. After that, however, while the therapy continued the readings climbed steeply. Apparently the patient had become quite refractory to stilboestrol in the dosage given. The oestrogen was stopped at the 30th week of pregnancy and restarted at the 31st week. Some degree of sensitivity appeared to have been re-established as a slight fall in the

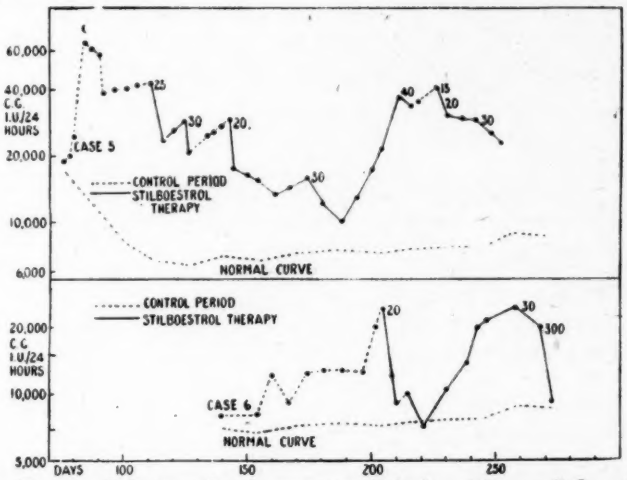


FIG. 3.—C.G. excretion in pregnant diabetics. The small figures denote doses (mg. per day) and are placed at the times these were started. (Cases 5 and 6).

excretion was obtained with a smaller dosage of stilboestrol. This patient was delivered by caesarean section at the 37th week. The weight of the baby was 6 lb. 1½ oz. (2.76 kg.) and of the placenta 1 lb. 2 oz. (0.51 kg.).

Case 6.—The rise in C.G. excretion in this patient occurred at the 24th week of pregnancy (Fig. 3), readings before that time being comparatively normal. Stilboestrol in dosage of 20 mg. a day was started at the 29th week. A transitory depression of the reading was obtained, but again the "escape" phenomenon was observed. A dose of 300 mg. given to induce labour approximately halved the C.G. reading. This patient was delivered by caesarean section at 41 weeks. The foetus weighed 9 lb. 4 oz. (4.2 kg.) and the placenta 1 lb. 15 oz. (0.88 kg.).

Case 7.—The excretion of C.G. was relatively normal in this patient until the 28th week of pregnancy, when a steep rise occurred (Fig. 4). Stilboestrol in dosage of 20 mg. a day was

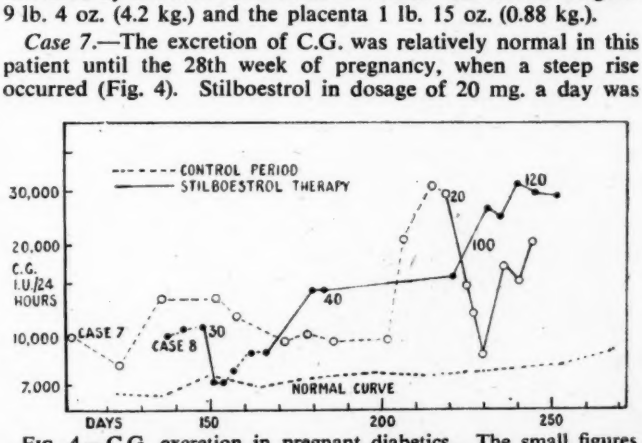


FIG. 4.—C.G. excretion in pregnant diabetics. The small figures denote doses (mg. per day) and are placed at the times these were started. (Cases 7 and 8).

started at the 31st week and produced a dramatic fall in the titre, but the reading climbed rapidly again while the therapy continued. This patient developed a mild degree of pre-eclampsia at 32 weeks. Delivery was by caesarean section at 34 weeks. The baby weighed 6 lb. 3 oz. (2.81 kg.) and the placenta 1 lb. 5 oz. (0.6 kg.).

Case 8.—Stilboestrol was administered to this patient at the 21st week of pregnancy for experimental purposes although the C.G. excretion was not unduly high (Fig. 4). A characteristic depression of the titre occurred, but the excretion rose when the treatment was stopped. No further readings were made until considerably later in pregnancy, when, although the patient was receiving massive doses of oestrogens (up to 120 mg. a day of stilboestrol supplemented by 100 mg. a day of oestradiol

benzoate at the 34th week), the C.G. level remained very high, again indicating refractoriness to the oestrogen. Delivery was by caesarean section at the 36th week of pregnancy. The foetus weighed 9 lb. 15¾ oz. (4.53 kg.) at birth and the placenta 2 lb. (0.9 kg.).

In Fig. 5 the results are shown in those pregnant diabetics in whom the excretion of C.G. was within normal limits.

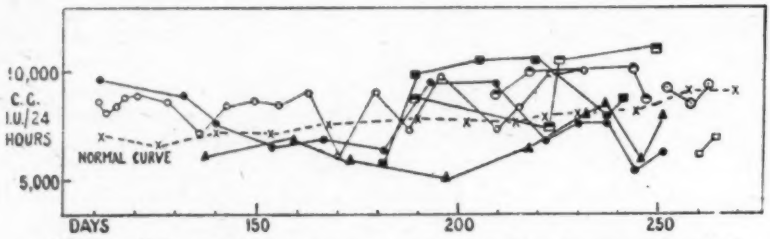


FIG. 5.—C.G. excretion in pregnant diabetics without hormonal therapy.

As in the previous series of normal cases, there is relatively little variation.

Discussion

From the evidence cited above it is apparent that a proportion of pregnant diabetic women (6 out of 14 studied) showed an abnormally high excretion of C.G. as compared with normally pregnant women. In the remaining eight diabetics the readings were perfectly normal (Fig. 5). Hormonal therapy was given only to those patients who after 100 days of gestation consistently showed a C.G. excretion of over 10,000 i.u. in 24 hours.

Stilboestrol when administered orally to normal and diabetic women, even in relatively small dosage, invariably produced a fall in the C.G. excretion. The degree of depression varied from case to case but tended to be more pronounced in early than in late pregnancy. On a constant dosage of the oestrogen, however, this depression was not maintained, the readings tending to climb back to their original level while the patient was still receiving treatment. This may be described as an "escape" phenomenon. At this stage an increase in dosage of stilboestrol temporarily produced another depression of the reading. Certain patients, however, seemed to become completely refractory to stilboestrol even in massive dosage. This is well illustrated by Case 8, which in the later stages of pregnancy was receiving 120 mg. of stilboestrol a day supplemented by oestradiol benzoate without depression of the C.G. level. There is some evidence (see Cases 3 and 5) that by cessation of the treatment for a few days sensitivity to the drug may be re-established and a depression of the C.G. level produced by a dose smaller than that previously employed.

The effect of stilboestrol on the C.G. excretion can therefore be considered to have five phases : (1) initial depression, (2) subsequent escape, (3) further depression by increase in dosage, (4) refractoriness after prolonged treatment, and (5) increased sensitivity to oestrogen on restarting treatment after stopping it for a few days.

The mechanism of action of oestrogens in producing these effects is not clear. Smith and Smith (1948), who first observed the rise in C.G., considered it a "compensatory" one due to lack of oestrogen and progesterone, and showed that oestrogen therapy will correct this.

Studies in the experimental animal have shown that oestrogen may suppress or inhibit the gonadotrophic activity of the anterior pituitary (Meyer and Biddulph, 1941 ; Meyer, Biddulph, and Finnerty, 1946). In the human, Jones and MacGregor (1936) observed that the injection of oestrogen into women at the menopause resulted in a cessation of the increased gonadotrophic hormone excretion in the urine, and Albright (personal communication to Professor J. H. Gaddum, September, 1948) obtained a depression of the follicle-stimulating hormone titres in the urine of menopausal women by the oral administration of stilboestrol. The rationale of oestrogen therapy in Cushing's syndrome (Dunn, 1938 ; Rakoff, Cantarow, and Paschkis, 1941) and in acromegaly (Schrire and Sharpey-Schafer, 1938 ; Goldberg and Lisser, 1942) is in virtue of the inhibitory effect produced on the anterior lobe of the pituitary. There does not appear, however, to be any previously published work on the effect of oestrogens in depressing the excretion of the gonadotrophic hormone elaborated by the placenta during pregnancy.

In the pregnant diabetics studied so far, no definite correlation has been found between the C.G. excretion on the one hand and the weight of the baby and placenta on the other. There also appeared to be no relation between the C.G. excretion and the insulin requirements during pregnancy in these patients.

Summary

Estimates have been made of chorionic gonadotrophin (C.G.) in the urine of 14 pregnant diabetics. The prostatic weight in immature rats was the end-point of the assay.

In 6 of these 14 cases the figures for C.G. excretion obtained were abnormally high when compared with that of normal women.

The administration of oestrogens caused an evanescent fall in the amount of C.G. excreted in the urine per 24 hours.

I am deeply indebted to Professor J. H. Gaddum for his help and guidance. I should like to thank Professor R. J. Kellar and Professor D. M. Dunlop for permission to study the cases under their charge. Thanks are also due to Dr. C. F. Rolland and Dr. G. D. Matthew for advice on the medical and obstetrical aspects of this paper. Finally, I am much indebted to Miss M. Mackay for the excellent technical assistance she has given me in carrying out the experiments.

REFERENCES

Astwood, E. B., and Jones, G. E. S. (1941). *J. biol. Chem.*, **137**, 397.
Barns, H. H. Fouracre, and Morgans, M. E. (1949). *British Medical Journal*, **1**, 51.
Boycott, M., and Rowlands, I. W. (1938). Ibid., **1**, 1097.
Browne, J. S. L., Henry, J. S., and Venning, E. H. (1939). *Amer. J. Obstet. Gynec.*, **38**, 927.
—— and Venning, E. H. (1936). *Lancet*, **2**, 1507.
Cole, H. H., and Saunders, F. J. (1935). *Endocrinology*, **19**, 199.
Dunn, C. W. (1938). Ibid., **22**, 374.
Gilbert, J. A. L., and Dunlop, D. M. (1949). *British Medical Journal*, **1**, 48.
Goldberg, M. B., and Lisser, H. J. (1942). *J. clin. Endocrinol.*, **2**, 477.
Herrick, W. W., and Tillman, A. J. B. (1938). *Surg. Obstet. Gynec.*, **66**, 37.
Jones, G. E. S., Delfs, E., and Stran, H. M. (1944). *Bull. Johns Hopk. Hosp.*, **75**, 359.
Jones, M. S., and MacGregor, T. N. (1936). *Lancet*, **2**, 974.
Kramer, D. W. (1935). *Amer. J. Obstet. Gynec.*, **30**, 68.
Lawrence, R. D., and Oakley, W. (1942). *Quart. J. Med.*, n.s. **11**, 45.
Loraine, J. A. (1949). *J. Endocrinol.* Vol. 6. In press.
Meyer, R. K., and Biddulph, C. (1941). *Amer. J. Physiol.*, **134**, 141.
—— —— and Finerty, S. C. (1946). *Endocrinology*, **39**, 23.
Rakoff, A. E. (1939). *Amer. J. Obstet. Gynec.*, **38**, 371.
—— Cantarow, A., and Paschkis, K. E. (1941). *J. clin. Endocrinol.*, **1**, 912.
Schrire, I., and Sharpey-Schafer, E. P. (1938). *Clin. Sci.*, **3**, 413.
Siegler, S. L. (1939). *J. Lab. clin. Med.*, **24**, 1277.
Smith, G. V. S., and Smith, O. W. (1935). *Surg. Gynec. Obstet.*, **61**, 27.
—— —— (1936). *New Engl. med. J.*, **215**, 908.
—— —— (1941). *J. clin. Endocrinol.*, **1**, 470.
—— —— (1948). *Physiol. Rev.*, **28**, 1.
—— —— and Hurwitz, D. (1944). *Amer. J. med. Sci.*, **208**, 25.

Taylor, H. C., and Scadron, E. N. (1939). *Amer. J. Obstet. Gynec.*, **37**, 963.
Venning, E. H. (1937). *J. biol. Chem.*, **119**, 473
— (1948). *Obstet. Gynec. Surv.*, **3**, 664.
Watts, R. M., and Adair, F. L. (1943). *Amer. J. Obstet. Gynec.*, **46**, 183.
White, P. (1937). Ibid., **33**, 380.
— (1943). *Va med. Mon.*, **70**, 436.
— (1946). In Joslin's *Treatment of Diabetes Mellitus*, 8th ed., p. 769. Kimpton, London.
— (1947). *Penn. med. J.*, **50**, 705.
— and Hunt, H. (1943). *J. clin. Endocrinol.*, **3**, 500.
— Titus, R. S., Joslin, E. P., and Hunt, H. (1939). *Amer. J. med. Sci.*, **198**, 482.

VITAMIN A, TOTAL CAROTENOIDS, AND THYMOL TURBIDITY LEVELS IN PLASMA

TEST IN NORMAL SUBJECTS RESIDING IN THE MIDLANDS DURING 1947

BY

DOROTHY ADAMS CAMPBELL, M.A., M.B., B.S.

AND

EVA L. TONKS, M.Sc.

(From the Research Department, Birmingham and Midland Eye Hospital, Birmingham)

In the course of a previous investigation into the cause of nystagmus in coal-miners we estimated the levels of vitamin A and total carotenoids in the plasma (Campbell and Tonks, 1948). Thymol turbidity tests were performed at the same time on a number of cases in order to exclude the possibility of liver dysfunction as a cause of fluctuation in these constituents. Since the diet of the majority of people had been rather drastically altered by war and post-war conditions in Great Britain, we were obliged to establish "normal" figures for comparison. It was thought that the values obtained might be of practical interest to other investigators engaged on similar problems.

Methods

Estimation of Vitamin A and Total Carotenoids in Plasma

Clausen's application of the Carr-Price colorimeter method was the means used in this procedure. The colour was measured in a Hilger absorptiometer, using filters specially designed for these estimations. The results were read off from standard curves prepared as suggested by Yudkin (1941).

The following reagents were used: (1) ethyl alcohol (redistilled); (2) petroleum ether (boiling point 40–60° C.); (3) chloroform—alcohol-free and dried over anhydrous sodium sulphate; (4) antimony trichloride solution 30% (w/v) in dry chloroform; this is a saturated solution freshly prepared and filtered, and is cleared of any turbidity by the addition of one drop of acetic anhydride.

Preparation of Standard Curves.—Carotenoids:—For this purpose pure β-carotene was obtained from the National Institute for Medical Research. A weighed amount (about 0.25 mg.) was dissolved in 100 ml. of petroleum ether (boiling point 40–60° C.). Aliquots of this solution were made up to 5 ml. with petroleum ether, and readings were taken in the absorptiometer to determine the standard curve for β-carotene, using the special filter combination provided by Hilger for carotenoids. *Vitamin A:*—Capsules of vitamin A alcohol of high purity were very kindly given to us by Roche Products, Ltd., to whom we offer our thanks. The contents of one capsule were weighed and made up to a known volume with chloroform. Under our conditions 1 ml. of this solution contained 27.25 i.u. Each aliquot taken was made up to 0.5 ml. with chloroform, and then 5 ml. of antimony trichloride solution was added. The resulting colour was read off on the absorptiometer within 10 seconds of the addition of the reagent, using the special combination of filters designed by Hilger for the estimation of vitamin A.

Correction Curve for the Blue Colour Produced by β-carotene and Antimony Trichloride.—A solution of a weighed quantity of β-carotene (1.2 mg.) was made up to 100 ml. with chloroform. Aliquots were made up to 0.5 ml., and 5 ml. of antimony trichloride solution was added. The special filter for vitamin A was used in the absorptiometer, and readings were taken within 10 seconds of mixing the reagents.

From these readings graphs were constructed so that results could be ascertained with accuracy and speed.

Two millilitres of plasma was placed in a stoppered centrifuge tube, 2 ml. of ethyl alcohol was added slowly, and the contents thoroughly mixed. To this mixture was added 4 ml. of petroleum ether. The stopper was inserted and the tube shaken at frequent intervals for half an hour. The mixture was then allowed to settle into its two layers or was centrifuged. An aliquot of the top layer (usually 3.6 ml.) was then transferred to an absorption cell, made up to 5 ml. with petroleum ether, and a reading taken using the carotenoid filter. The equivalent value in terms of β-carotene was then obtained from the standard curves and calculated for 100 ml. of plasma.

The petroleum ether solution in the cell was evaporated to dryness by placing the cell in a bath of warm water (40–60° C.). A gentle current of dry air or nitrogen was used to assist evaporation. The residue was dissolved in 0.5 ml. of dry chloroform. With the use of the special vitamin-A filter the cell was placed in the rack of the absorptiometer and 5 ml. of antimony trichloride solution added. The reading was taken within 10 seconds of the addition of the reagent.

The amount of vitamin A present in the cell was calculated by reading the value from the standard curve for vitamin A and subtracting the amount of blue colour due to the reaction of the antimony trichloride with the estimated amount of carotenoids present. From this value the amount in 100 ml. of plasma was calculated.

Thymol Turbidity Test

This test was originally described by Maclagan (1944), but in order to get more precise comparable values the modification of Ley, Lewis, and Davidson (1946) was used, in which a barium sulphate suspension was employed as a standard and the turbidity was measured in the Hilger absorptiometer. The results given in this paper, therefore, are expressed as being equivalent to the corresponding amount in millilitres of barium sulphate suspension.

A slight modification was introduced—namely, the performance of a blank test with 0.1 ml. of plasma and 6 ml. of 0.9% sodium chloride. The reading of this blank test on the standard barium sulphate suspension curve was subtracted from the value obtained in the usual way in the case of lipaemic or slightly haemolysed plasma.

Results

Vitamin A and Total Carotenoids

Our series consisted of 133 normal adults (116 men and 17 women) varying in age from 18 to 73 years. They included housewives, office workers, factory hands of all types, and labourers, and came from all walks of life. They were tested only when free from infection, as Brenner and Roberts (1943) found that feverish colds reduced the blood level of vitamin A by one-half. All specimens of blood were collected at approximately three hours after

a meal, but no attempt was made to obtain fasting specimens, since Kimble (1939) found that ordinary meals do not cause a measurable increase in either vitamin A or carotene within two to six hours.

The figures in our 133 subjects were:

Total carotenoids (μg./100 ml.)	20–199	Mean	80
Vitamin A (i.u./100 ml.)	69–158	,,	108

These figures are strikingly different from those of Haig and Patek (1942) in America, based on 74 measurements on 44 normal people between the ages of 20 and 45:

Total carotenoids (μg./100 ml.)	69–240	Mean	144
Vitamin A (i.u./100 ml.)	109–309	,,	198

It is to be noted that all these subjects were on highly nutritious diets which were estimated to provide at least 13,000 i.u. of vitamin A daily.

Yudkin (1941) in England, in a series of 23 normal adults varying from 18 to 30 years of age, found:

Total carotenoids (μg./100 ml.)	50–240	Mean	120
Vitamin A (i.u./100 ml.)	72–157	,,	113

while Moore and Leitner, during the course of an investigation of the vitamin A requirement of human adults, published in the Medical Research Council Special Report No. 264 (1949), collected a series of 195 cases, comprising 112 subjects with illnesses not expected to affect the vitamin A value, and 83 normal subjects. They give the following figures as their mean values:

	All Cases	Normals
Total carotenoids (μg./100 ml.)	92	100
Vitamin A (i.u./100 ml.)	121	128

Their series was collected from residents in the London area in 1946, while ours, collected during 1947 in the Midlands, are lower than these, both in carotenoids and in vitamin A levels.

The long-continued low intake of fat due to rationing restrictions accounts for the fact that our standards for the average blood level of carotenoids and vitamin A in this country are lower than those considered normal by American standards. This must be borne in mind when assessing the nutritional state of persons suffering from disease.

Variation with Age.—Taking our cases in approximately 10-year age groups, the total carotenoids and vitamin A figures show a slight variation with age (Table I).

Influence of Season.—There was a slight fluctuation in the vitamin A values when grouped in two-monthly periods throughout the year, while the carotenoids showed a steady rise from March/April to November/December (Table III).

TABLE III.—*Seasonal Variation in Total Carotenoid and Vitamin A Content of Blood Plasma*

	Jan. Feb.	Mar. Apr.	May June	July Aug.	Sept. Oct.	Nov. Dec.
Total carotenoids (μg./100 ml.)	82	65	69	75	82	97
Vitamin A (i.u./100 ml.)	110	94	108	113	108	112

Influence of Occupation.—The cases investigated have been grouped into four categories to see if any difference in carotenoid and vitamin A blood levels resulted from hard physical exercise and consequent increased metabolism (Table IV). The "heavy" category of occupation in this series included all those people who do hard manual labour, with the exception of coal-miners. An additional group of 133 miners (divided into "surface" and "underground" workers) shows figures comparable with those for other heavy industries, the levels being particularly low in miners working underground (Table V).

TABLE IV.—*Influence of Occupation on Total Carotenoid and Vitamin A Content of Blood Plasma*

	Occupation			
	Heavy	Medium	Light	Sedentary
Total carotenoids (μg./100 ml.)	76 (37 cases)	79 (34 cases)	88 (32 cases)	81 (30 cases)
Vitamin A (i.u./100 ml.)	102	109	111	113

TABLE V.—*Variation of Total Carotenoid and Vitamin A Content of Blood Plasma in Coal-miners*

	Miners, Surface	Miners, Underground
Total carotenoids (μg./100 ml.)	72 (53 cases)	67 (80 cases)
Vitamin A (i.u./100 ml.)	102	97

Thymol Turbidity Tests

Thymol turbidity tests were performed on 110 normal adults, giving values varying from 0.2 to 1.85 ml. of barium sulphate suspension with a mean value of 0.59. Ley, Lewis, and Davidson (1946), in a series of 105 healthy young men, found a range of 0.16 to 2.19 ml. with a mean value of 0.63. In our series 84% of the cases had a value of less than 0.9 ml. and 93% a value of less than 1.06 ml. of barium sulphate suspension, while less than 3% had values exceeding 1.5 ml.

It is suggested that the introduction of the blank reaction into this estimation has the effect of reducing the upper limit of the normal range, and that the true range should be 0 to 1.5 ml. of barium sulphate suspension.

TABLE I.—*Age Variation in Total Carotenoid and Vitamin A Content of Blood Plasma*

	18–29 Years		30–39 Years		40–49 Years		50–59 Years		60–73 Years	
	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean
Total carotenoids (μg./100 ml.)	20–118	70 (26)	42–199	80 (32)	26–137	80 (26)	40–192	90 (24)	23–190	83 (25)
Vitamin A (i.u./100 ml.)	69–148	106 (26)	84–141	112 (32)	82–158	110 (26)	75–145	109 (24)	80–138	105 (25)

Figures in parentheses indicate the number of cases.

Influence of Sex.—Our series is predominantly male, but the results show the same trend as that found by Kimble (1939) and by Moore and Leitner, in that the carotenoids are higher in females than in males, while the vitamin A is slightly lower in females than in males (Table II).

TABLE II.—*Total Carotenoid and Vitamin A Content of Blood Plasma in Males and Females*

		Total Carotenoids (μg./100 ml.)			Vitamin A (i.u./100 ml.)		
		Range	Mean	No. of Cases	Range	Mean	No. of Cases
Our series	Males	20–199	79	116	69–158	109	116
	Females	52–155	90	17	75–155	105	17
Kimble, 1939	Males	50–300	166	30	87–193	127	30
	Females	90–340	187	34	65–165	91	34
M.R.C., 1949	Males		96	46		146	46
	Females		105	37		110	37

Conclusions

Our cases were collected from patients attending eye clinics for minor accidents, for refraction, or for correction of squint. They may be regarded as a cross-section of the

population of the Midlands, having no obvious disease or chance infection. This being so, our results show that the average blood levels of the total carotenoids and vitamin A are lower in this part of England than those found in other countries.

In the Medical Research Council's Special Report on Vitamin A Requirements of Human Adults are assembled all the available data on the normal value for the carotenoid and vitamin A content of human blood plasma in 195 subjects, and Moore and Leitner, who carried out the investigation, point out that some American authors, in calculating the values for vitamin A, do not appear to have made any correction for the blue colour contributed by carotenoids to the antimony trichloride reaction. They also state that some of the earlier workers in America used the U.S.P. unit, which is now held by Hume (1943) to have only 87% of the value of the international unit, and that it is not always possible in retrospect to be certain which unit was really meant.

These facts may account for the apparent discrepancies between American and English results, as well as the fact that the people of Britain do not have access to unlimited fat, and have not acquired the taste for large quantities of green vegetables and salads. In our series 85% of cases have total carotenoid plasma levels lying between 40 and 120 μg./100 ml., and vitamin A plasma levels between 80 and 130 i.u./100 ml., and these are suggested as being reasonable limits for normality under conditions prevailing in the Midland area of England during 1947.

The results of our investigation indicate slightly lower levels for vitamin A, and considerably lower levels in total carotenoids, compared with those found by other English workers (Yudkin, 1941 ; M.R.C., 1949).

Summary

The levels of total carotenoids and vitamin A in the plasma of 133 normal adults were estimated. The investigation took place throughout the year 1947. The normal range was found to be:

Total carotenoids (μg./100 ml.)	20–199	Mean	80
Vitamin A (i.u./100 ml.)	69–158	,,	108

but since 85% of our cases gave values of

Total carotenoids (μg./100 ml.)	40–120
Vitamin A (i.u./100 ml.)	80–130

these are suggested as limits of normality under conditions prevailing in the Midland area of England in the year 1947.

Vitamin A levels showed a slight fluctuation during the year, while the level of the total carotenoids rose steadily from March to December.

Those subjects performing hard manual labour showed lower levels of total carotenoids and vitamin A than subjects engaged in light or sedentary occupations.

Thymol turbidity tests were performed on a series of 110 normal adults, and it was found that when allowance is made for a "blank" test the normal range is 0 to 1.5 ml. of barium sulphate suspension, with a mean value of 0.59 ml.

REFERENCES

Brenner, S., and Roberts, L. J. (1943). *Arch. intern. Med.*, **71**, 482.
Campbell, D. A., and Tonks, E. (1948). *Brit. J. Ophthal.*, **32**, 205.
Haig, C., and Patek, A. J. (1942). *J. clin. Invest.*, **21**, 377.
Hume, E. M. (1943). *Nature, Lond.*, **151**, 535.
Kimble, M. S. (1939). *J. Lab. clin. Med.*, **24**, 1055.
Ley, A. B., Lewis, J. H., and Davidson, C. S. (1946). Ibid., **31**, 910.
Maclagan, N. F. (1944). *Nature, Lond.*, **154**, 670.
Medical Research Council (1949). Spec. Rep. Ser. No. 264. H.M.S.O., London.
Yudkin, S. (1941). *Biochem. J.*, **35**, 551.

CHLORAMPHENICOL IN TREATMENT OF INFANTILE GASTRO-ENTERITIS

A PRELIMINARY REPORT

BY

K. B. ROGERS, M.D.
Clinical Pathologist

S. J. KOEGLER, M.D.
Registrar

AND

JOHN GERRARD, B.M., M.R.C.P.
Lecturer in Paediatrics at the University of Birmingham

(From the Children's Hospital, Birmingham)

Bray (1945), Giles and Sangster (1948), and Taylor *et al.* (1949) independently noted a close correlation between the same serologically specific type of *Bact. coli* and epidemic infantile gastro-enteritis. This *Bact. coli* is referred to in this communication as *Bact. coli* B.G.T. (Bray–Giles–Taylor).

During the last ten months one of us (K. B. R.) has studied the appearance of this organism in 86 infants under the age of 1 year admitted to the Birmingham Children's Hospital. Routine rectal swabs were taken on admission and in many cases five days later, and again if a case of gastro-enteritis appeared in the ward. The first isolation of the *Bact. coli* B.G.T. from the stool was noted and the subsequent progress of the infant observed.

Epidemiology

In 17 cases it was possible to calculate the interval between the time of the first isolation of this organism from the faeces and the development of a gastro-intestinal disturbance. In all cases except one this period was less than 22 days; the exception was a case which developed diarrhoea at home 24 days after the first positive rectal swab. The shortest interval was four days, in two cases; the average interval was 11 days. It must be emphasized that in 25 of the 86 cases observed the appearance of the *Bact. coli* B.G.T. in the faeces was followed by no untoward symptoms; these cases were followed for a period of at least one month.

This organism was isolated from the stools of 86 babies under the age of 1 year, 82 of whom acquired the organism after admission to hospital; 25 patients, 10 of whom were less than 4 months old, had no intestinal symptoms, while the remaining 61 developed gastro-intestinal disturbances which varied from a severe gastro-enteritis to a mild diarrhoea with or without vomiting; of these 61 patients 13 died. All of the deaths occurred in infants under the age of 4 months, except in two who were aged 10 months. One of the two, a mongoloid idiot, collapsed and died directly after discharge from hospital, but to what extent the *Bact. coli* was responsible is not known. The other, a case of pink disease, died primarily of respiratory failure associated with an extensive polyneuritis and diaphragmatic palsy, but she also had a severe terminal enteritis. The finding that *Bact. coli* B.G.T. is more commonly associated with severe gastro-enteritis in the younger babies is in agreement with the observations of Taylor *et al.* (1949). That the appearance of *Bact. coli* B.G.T. in the stools is sometimes associated with a fulminating gastro-enteritis is suggested by such typical case histories as the following.

Case 1.—A girl aged 3 months was admitted with pseudo-paralysis due to congenital syphilis, for which she received penicillin. A month after admission *Bact. coli* B.G.T. was isolated from the faeces; 15 days later, after her transfer to another hospital for further antisyphilitic treatment, she developed diarrhoea. Four days after the onset she collapsed and died.

Case 2.—A girl aged 2 months was admitted with cystic fibrosis of the pancreas. Her progress was satisfactory at first, but five days after *Bact. coli* B.G.T. was isolated from the stools she developed a watery diarrhoea and 10 days later she died. Necropsy revealed fibrocystic dystrophy of the pancreas complicated by enterocolitis, bronchopneumonia, adhesive pleurisy, and right otitis media; clinically the severe gastro-enteritis was the cause of her sudden death.

Case 3.—A girl aged 1 month was admitted because she had vomited with increasing severity since birth and had become jaundiced. Diarrhoea was present on admission and the stools contained *Bact. coli* B.G.T. In spite of intravenous alimentation the gastro-enteritis persisted and she died 13 days later.

Case 4.—A girl aged 1 month was admitted with generalized convulsions precipitated by an otitis media. From this she made an uneventful recovery. Four days after admission *Bact. coli* B.G.T. was isolated from the stools; 10 days later gastro-enteritis developed and after nine days she died. Necropsy revealed a haemorrhagic enterocolitis with intestinal pneumatosis and an early peritonitis.

Treatment with Penicillin and Sulphonamides

All cases of severe gastro-enteritis were treated as a routine with intravenous alimentation until the diarrhoea and dehydration were controlled, followed by graded oral feeding. Initially, penicillin and sulphonamides were also administered. These agents helped to control parenteral infections, such as otitis media, but they seemed to have little or no direct effect on the gastro-enteritis. In fact, *Bact. coli* B.G.T. appeared in the stools and gastro-enteritis developed in some cases while the infant was actually receiving both penicillin and sulphonamides. Case 5 is an example.

Case 5.—A girl aged 6 months was admitted with scalded buttocks, and developed gastro-enteritis associated with the isolation of *Bact. coli* B.G.T. while on penicillin, sulphonamides, and streptomycin.

In no case did either penicillin or sulphonamides remove *Bact. coli* B.G.T. from the stools once this organism had made its appearance.

Treatment with Streptomycin

Streptomycin proved to be equally disappointing in its failure to cure gastro-enteritis. Although only 12 cases were treated with this drug, four orally and the remainder by intramuscular injection, the results did not appear to justify further investigation. Our small experience supports that of Holzel *et al.* (1949) and not that of James *et al.* (1948). In Holzel's series 50 of the 79 cases were associated with *Bact. coli* B.G.T., but this organism was not mentioned by James *et al.*, whose cases might therefore have had a different aetiological agent.

In three of our cases which received streptomycin *Bact. coli* B.G.T. was actually isolated from the faeces for the first time while streptomycin was being given for other conditions (miliary tuberculosis, a large infected naevus, and infected scalds of buttocks). Two of these cases developed a severe gastro-enteritis necessitating intravenous alimentation; the third had no more than a mild diarrhoea preceded by a loss of weight. Of the remaining nine patients one died, a second deteriorated whilst on streptomycin, and seven recovered, but only one made a quick recovery. *Bact. coli* B.G.T. disappeared from the stools of only one child while it was receiving streptomycin.

Chloramphenicol

When it was decided to investigate the efficacy of one of the newer antibiotics, chloramphenicol ("chloromycetin") was chosen because all strains tested were sensitive to this drug; they were also sensitive to "aureomycin," but chloramphenicol was used because of its relative stability. Chloramphenicol was first described by Ehrlich *et al.* (1947), who mentioned that *Bact. coli* was sensitive to it. It is felt that the results with this

Table Showing Cases Treated with Chloramphenicol

Case	Sex	Age in Months	Reason for Admission	Days After Admission Before Onset of G.E.	Severity	Duration of Treatment with Chloramphenicol in Days	Complications	I.V. Alimentation	Days Taken to Clear *Bact. coli* B.G.T.	Result	Comments
S.B.	F	6	Scalds of buttocks	13	Severe	13	Infected scalds and G.E.	Yes	5	Died	Died 9 days after disappearance of *Bact. coli* B.G.T. from stools but after diarrhoea had ceased
M.C.	M	2	Otitis media	18	Severe	15	None	Yes	3	Survived	
G.H.	M	8	Pink disease	On readmission	Moderate	10	Sore buttocks	No	3	"	Readmitted with G.E. 10 days after discharge from original admission for nutritional disorder and pink disease
N.H.	M	3	Otitis media	11	Severe	10	Mastoiditis	No	2	"	
J.M.	F	1	Marasmus	12	Severe	11	Sore buttocks	Yes	3	"	Bacteriological relapse 7 days after cessation of chloramphenicol. Had been clear 15 days
R.M.	M	1	Pyloric stenosis	17	Moderate	9	None	No	?	"	
L.P.	F	5	G.E.	On admission	Severe	7	Staphylococcal septicaemia and osteomyelitis	Yes	3	"	Bacteriological relapse 1 day after cessation of chloramphenicol; had been clear for 5 days
W.R.	F	4½	Thrush and parotitis	11	Severe	13	Sore buttocks	Yes	5	"	
D.S.	M	5	G.E.	On readmission	Severe	14	None	Yes	7	"	Readmitted with G.E. 4 days after discharge from original admission for otitis media and asthma
R.S.	M	8	Pink disease	15	Moderate	12	"	No	8	"	
S.S.	F	5	G.E.	On admission	Moderate	13	"	No	3	"	Discharged from another hospital 8 days before admission
D.T.	M	1½	Meningitis	40	Severe	14	Sore buttocks	Yes	4	"	
J.C.	F	3	Prematurity	On readmission	Severe	13	Otitis media	Yes	5	"	(Twin died of G.E. associated with *Bact. coli* B.G.T. and received no chloramphenicol.) Readmitted with G.E. 13 days after discharge from original admission for otitis media
J.N.	M	2½	G.E.	On admission	Mild	6	None	No	3	"	Attending a day nursery
J.P.	F	2	Marasmus	27	Mild	9	"	No	Never	"	

J.C., J.N., and J.P. were carriers who had recovered from their initial G.E., but who still excreted *Bact. coli* B.G.T. G.E. = Gastro-enteritis.

antibiotic are hopeful enough to warrant a preliminary communication, although it is realized that the number treated is small. The age groups in the different series are not strictly comparable; moreover, individual cases vary so much in severity that, with small numbers, comparisons are invidious. These results can best be illustrated by the following case histories. (For further details of cases see table.)

Case 5 (already referred to).—In spite of treatment with sulphonamides, penicillin, and streptomycin her gastro-enteritis continued, but within five days of starting chloramphenicol *Bact. coli* B.G.T. disappeared from the stools and the diarrhoea ceased. Unfortunately she died from complications due to burns nine days after the disappearance of *Bact. coli* B.G.T. from the faeces. A post-mortem examination was not made.

Case 6.—A boy aged 5 weeks was admitted with meningococcal meningitis. Nineteen days after the first appearance of *Bact. coli* B.G.T. in the stools, and while receiving both sulphonamides and penicillin, he developed a severe gastro-enteritis. No improvement followed the administration of streptomycin, but within three days of starting chloramphenicol therapy the diarrhoea ceased; a day later *Bact. coli* B.G.T. disappeared from the stools. Further recovery was uneventful.

Case 7.—A boy aged 8 months was admitted with pink disease. Fifteen days after admission he developed gastro-enteritis associated with the isolation of *Bact. coli* B.G.T. from the faeces. With penicillin and sulphonamide therapy there was little improvement, but on chloramphenicol the organism disappeared within eight days, the diarrhoea ceased, and he started to gain weight satisfactorily.

Case 8.—A girl aged 4½ months was admitted with thrush and a left parotitis. The infection subsided with the application of gentian violet locally and penicillin systemically, but 10 days after the isolation of *Bact. coli* B.G.T. from the stools she developed diarrhoea and lost 12 oz. (340 g.) in weight in three days. The enteritis did not respond to symptomatic treatment, but when chloramphenicol was given the diarrhoea ceased; *Bact. coli* B.G.T. disappeared from the stools in five days.

In eight additional cases the administration of chloramphenicol, in conjunction with intravenous alimentation where necessary, and graded feedings, was followed by rapid amelioration of the diarrhoea, and *Bact. coli* B.G.T. could no longer be recovered from the faeces. In three cases there was a bacteriological relapse, although no case had a recurrence of the diarrhoea.

Carriers.—Three children who had had diarrhoea associated with the presence of *Bact. coli* B.G.T. but had recovered from their diarrhoea still excreted this organism in the faeces. They were given chloramphenicol. In one case *Bact. coli* B.G.T. was not recovered from the faeces after the third day of treatment. In a second the organism was not recovered from the fifth day of treatment until four days after the cessation of treatment, when a bacteriological relapse occurred. In the third case this organism was still present in the faeces after nine days' treatment.

Clearance of the Organism.—The average time for chloramphenicol to effect a clearance of *Bact. coli* B.G.T., except in the carriers already mentioned, was four days, within the limits of two and eight days. In two cases the organism reappeared in the faeces one and seven days after cessation of treatment which had lasted seven to eleven days respectively, but the organisms were still sensitive to chloramphenicol. These cases may have been either true relapses or reinfections, as neither had been discharged from the infected ward.

Parenteral Infection.—Six cases were admitted with an otitis media. No *Bact. coli* B.G.T. were isolated from their faeces, but before these infants were fit for discharge they had not only acquired the organism but had also developed gastro-enteritis. It is understandable that, in the absence of recognition of any organism as a potential pathogen in the stools, the diarrhoea might be ascribed to the inflammation in the ears. In point of fact, the sequence of events would seem to have been an initial infection necessitating admission to hospital, followed by a subsequently acquired intestinal infection. An otitis media was present at the onset of the gastro-enteritis in two cases; in three additional cases an otitis media developed from five to ten days after the onset of the gastro-intestinal infection. In no case was *Bact. coli* B.G.T. isolated from the middle ear.

Other Cases

Case 9 is worthy of special mention as it was the only one in which a primary urinary infection with *Bact. coli* B.G.T. was encountered.

Case 9.—A boy aged 7 weeks was admitted with anaemia, mild jaundice which developed during the week before admission, severe urinary-tract infection, and bilateral otitis media. The urine contained many pus cells, casts, and a few red cells, and gave a heavy pure growth of *Bact. coli* B.G.T. There was no evidence of any abnormality in the blood apart from anaemia. Gastro-enteritis developed three days after admission, but *Bact. coli* B.G.T. were not isolated from the faeces. The urinary infection was not influenced by penicillin, given on account of the otitis media, or by sulphonamides, but responded dramatically, as did the enteritis, to chloramphenicol.

Bact. coli B.G.T. may be associated with diarrhoea in older children; the oldest child known to be affected in this hospital was a girl 4 years old, and although, because of her age, she is not included in this series, her case history is of considerable interest. Soon after she had successfully negotiated a Blalock–Taussig operation she developed severe enteritis in which the only potential pathogenic organism that could be isolated was *Bact. coli* B.G.T. After three days' treatment with chloramphenicol, given for seven days, the diarrhoea ceased and *Bact. coli* B.G.T. was no longer isolated from the stools. Before this case occurred no gastro-intestinal disturbance associated with the presence of *Bact. coli* B.G.T. had been discovered in the general wards of this hospital. The enteritis in this 4-year-old girl began 15 days after a baby who was excreting the organism had been transferred to her ward.

Administration of Chloramphenicol

Chloramphenicol is marketed in 250-mg. enteric-coated capsules, but as infants cannot swallow these the drug has been given as a suspension with tragacanth flavoured with syrup of raspberry and chloroform water. The babies have needed little encouragement to take it in spite of its bitter taste. The dosage given has been 75 mg. per lb. (165 mg. per kg.) body weight per day in six or eight divided doses; the initial dose was twice the maintenance dose.

Complications of Chloramphenicol Therapy

The administration of chloramphenicol has occasionally coloured the stools bright green. Four of the cases developed sore buttocks followed by a spreading generalized dermatitis which cleared only after two weeks, but it is not established that chloramphenicol was responsible. Apart from this possible toxic reaction, no untoward effects have been noted; routine blood counts and urine examinations on all cases have shown no abnormalities.

Further Investigation

A trial with chloramphenicol is now being undertaken on all severe cases of infantile gastro-enteritis, irrespective of the presence of the known specific strains of *Bact. coli*. Although *Bact. coli* B.G.T. is often associated with gastro-enteritis there is no proof of its actual pathogenicity, and, moreover, a number of babies who excrete this specific strain of *Bact. coli* never develop symptoms: there may

have been a previous undetected infection with *Bact. coli* B.G.T. in these cases. On the other hand, an appreciable number of children are admitted with primary gastro-enteritis without any identifiable specific strain of *Bact. coli* in their faeces.

Bacteriology

Routine Examination.—Faeces from cases of gastro-enteritis were examined to exclude the presence of protozoa and cultured on Leifson's desoxycholate citrate medium as well as in selenite enrichment medium to exclude the presence of salmonellae and shigellae. A MacConkey plate was also inoculated and at least four representative colonies were tested by slide agglutination, using Bray and Beavan's (1948) technique, which gave very clear-cut and reliable results. All positive colonies were inoculated into sugars, and a culture was sent to Dr. Joan Taylor, who very kindly confirmed their identity.

Sensitivity of the Organism to Chloramphenicol.—Bact. coli B.G.T. was inhibited in concentrations of chloramphenicol varying between 2 to 4 μg./ml. Tests were made using representative colonies from each specimen from which *Bact. coli* B.G.T. was isolated whilst the child was on chloramphenicol treatment or if the organism reappeared after treatment had been stopped. No change in sensitivity of the organism was shown in these experiments. This is in agreement with the work of Smadel *et al.* (1949) and Alexander *et al.* (1949). This result is very different from those obtained with streptomycin, when insensitive variants began to appear in nearly all cases within 24 hours of the initiation of treatment. In most of the antibiotic-treated cases specimens of faeces were obtained once or twice daily during treatment and daily for two weeks after its cessation or until the patient was discharged.

Blood Levels.—Estimations of chloramphenicol blood levels were made; the technical difficulties were not fully overcome, but by the use of a modification of the technique described by Fleming and Smith (1947) levels up to 120 μg./ml. were obtained. The test organism used was a strain of *Bact. coli* B.G.T. from Case 5. There seemed to be definite individual variations in the absorption of the drug by the patient, so a relatively high dose of chloramphenicol was employed.

Summary

In Birmingham, as in many other parts of Great Britain where it is sought, *Bact. coli* B.G.T. has been found to be intimately associated with epidemic infantile gastro-enteritis. The enteritis did not respond to the administration of sulphonamides, penicillin, or streptomycin, but the response, both clinically and bacteriologically, to chloramphenicol has been most encouraging.

We would like to express our thanks to the staff of the Children's Hospital, Birmingham, especially to Professor J. M. Smellie for his encouragement and most valuable criticism, to Sister M. Coker for her co-operation, and to Dr. Joan Taylor for much advice and help; also to Dr. C. Giles, who supplied the first antisera used in this investigation.

REFERENCES

Alexander, H. E., Leidy, G., and Redman, W. (1949). *J. clin. Invest.*, **28**, 867.
Bray, J. (1945). *J. Path. Bact.*, **57**, 239.
—— and Beavan, T. E. D. (1948). Ibid., **60**, 395.
Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, P. R. (1947). *Science*, **106**, 417.
Fleming, A., and Smith, C. (1947). *Lancet*, **1**, 401.
Giles, C., and Sangster, G. (1948). *J. Hyg., Camb.*, **46**, 1.
Holzel, A., Martyn, G., and Apter, L. (1949). *British Medical Journal*, **2**, 454.
James, U., Kramer, I. R. H., and Armitage, P. (1948). *Lancet*, **2**, 555.
Smadel, J. E., Woodward, T. E., and Bailey, C. A. (1949). *J. Amer. med. Ass.*, **141**, 129.
Taylor, J., Powell, B. W., and Wright, J. (1949). *British Medical Journal*, **2**, 117.

PARATYPHOID B FEVER TREATED WITH CHLORAMPHENICOL

BY

MICHAEL CURTIN, M.D., M.R.C.P.I., D.P.H.
Registrar, Sheriff Hill Infectious Diseases Hospital, Gateshead-on-Tyne

The clinical course of paratyphoid fever is subject to much variation. Compared with typhoid fever it is in general a milder disease, although attacks of paratyphoid fever occur which both in severity and in duration rank with typhoid even of the most severe form. Owing to this variation in degree of clinical illness it is difficult to assess the response to any particular form of treatment. Reports on paratyphoid B fever treated with chloramphenicol (chloromycetin) have been few. Christie (1949) has reported briefly on seven cases, and Kiledjian (1949) and Montuschi (1949) have each reported on a single case. As much investigation remains to be done before the full effect of the drug on paratyphoid fever can be finally assessed, and as it will be some time before an optimum scheme of dosage can be arrived at, the following report may be of interest.

Betweeen June and October, 1949, six clinical cases of moderately severe paratyphoid B fever were admitted to Sheriff Hill Infectious Diseases Hospital. The diagnosis was confirmed in all cases by culture of *Salmonella paratyphi B*. All patients had been ill for some days before admission; treatment with chloramphenicol was started in three cases at the end of the first week, in two cases during the second week, and in the sixth case early in the third week of disease. The dosage and the period of administration of the drug varied, patients who were admitted later in the series receiving larger doses over a longer period. The frequency of administration remained constant, the drug being given at four-hourly intervals.

In addition to the above cases, three apparently healthy faecal carriers of *Salm. paratyphi B* were admitted and treated with chloramphenicol.

Case 1

A girl aged 11 was admitted on June 21, 1949, complaining of malaise, headache, anorexia, diarrhoea, and abdominal pain of five days' duration.

On examination she was obviously toxic, cerebration was dull, her mouth was dry, and her tongue was heavily furred. The abdomen was tumid and slightly tender. The spleen was just palpable. Her temperature was 99.4° F. (37.4° C.) and pulse 120.

Progress and Treatment.—On admission penicillin (200,000 units four-hourly) and sulphasuxidine (8 g. daily) were given and continued for five days. There was no improvement: diarrhoea, abdominal pain and tenderness, pyrexia, and drowsiness persisted. *Salm. paratyphi B* phage type 3A was cultured from faeces. On the tenth day of disease a course of chloramphenicol was

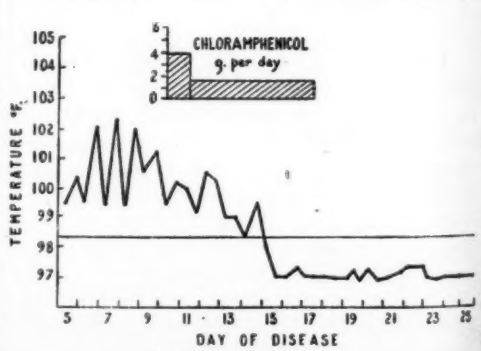


Chart 1.—Case 1.

started (1 g. in first hour, 0.5 g. four-hourly for 24 hours, and then 0.25 g. four-hourly for six days). On the following day the patient's general condition was improved and she was much brighter mentally. Within 48 hours diarrhoea and abdominal tenderness disappeared. Her temperature was normal in four days (Chart 1). There was no clinical relapse, but *Salm. paratyphi B* was excreted in faeces for six weeks after clinical recovery. *In vitro* tests showed that the infecting organisms were sensitive to chloramphenicol even when the temporary carrier state had developed.

Case 2

A woman aged 29 was admitted on July 1, 1949, with a history of the onset of headache, pyrexia, abdominal discomfort, and constipation 14 days previously. At the time of admission her only complaint was that of general weakness and fatigue. On examination her temperature was 100° F. (37.8° C.) and pulse 102. The tongue was furred, and there was evidence of recent wasting. A mitral systolic murmur was heard, but nothing else abnormal was found.

Progress and Treatment.—After admission the patient progressed favourably for three days. *Salm. paratyphi* phage type 3A was isolated from faeces. On the fourth day there was a sudden rise in temperature accompanied by headache, abdominal discomfort, and mild abdominal tenderness. As it was felt that a relapse had taken place, next day she was given chloramphenicol (1 g. in first hour, 0.5 g. four-hourly for 24 hours, and then 0.25 g. four-hourly for five days). Treatment coincided with general improvement. Her temperature did not show a dramatic response, returning to normal on the fourth day of treatment. A convalescent carrier state developed, and this persisted for eight weeks.

Case 3

A boy aged 5 was admitted on July 6, 1949, with a history of lassitude, anorexia, cough, abdominal pain, and diarrhoea.

On examination he was obviously toxic, drowsy, and irrational, and had bouts of noisy delirium. His tongue was heavily furred. The abdomen was distended, and palpation was resented. The spleen was moderately enlarged. A few rose-coloured spots were present on the abdomen. His temperature was 101.8° F. (38.8° C.) and pulse 98.

Progress and Treatment.—On admission on the seventh day of illness a course of chloramphenicol was started (0.25 g. four-hourly for six days). Next day there was a remarkable change in the patient's condition. He was alert and composed, and the abdomen was less tender. Within 48 hours diarrhoea had ceased. His temperature returned to normal on the third day of treatment (Chart 2), coincident with clinical recovery. *Salm. paratyphi* phage type 3A was cultured from specimens of blood and faeces taken on the day of admission. A convalescent faecal carrier state developed and lasted for nine weeks.

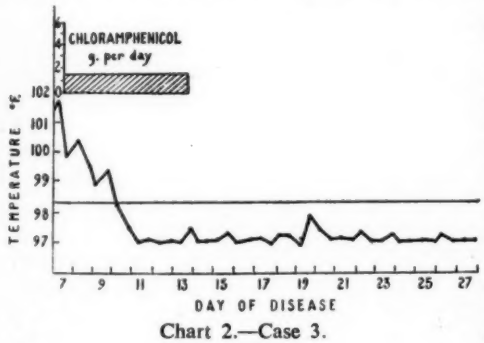


Chart 2.—Case 3.

Case 4

A boy aged 6 was admitted on July 18, 1949, with a history of headache, vomiting, drowsiness alternating with restlessness, and constipation.

On examination his general condition was fair, his tongue was furred, the abdomen was tumid, and a few rose-coloured spots were seen on his abdomen and legs. His temperature was 100.6° F. (38.1° C.) and pulse 112.

Progress and Treatment.—On admission on the seventh day of illness he was put on a course of chloramphenicol (0.5 g. four-hourly for 24 hours and 0.25 g. four-hourly for four days). On the morning following admission several fresh rose-coloured spots were noted. However, his general condition was much improved. The temperature settled to normal in 24 hours. *Salm. paratyphi* phage type 3A was isolated from specimens of blood and faeces taken on the day of admission. The patient continued to excrete the infecting organisms in faeces for seven weeks after termination of treatment.

Case 5

A woman aged 40 was admitted on August 27, 1949, with a history of headache, generalized abdominal pain, constipation, and malaise for six days.

On examination cerebration was dull and speech was sluggish. There was well-marked abdominal tenderness. The tongue was furred. The temperature was 101° F. (38.3° C.) and pulse 92. There were no other abnormal findings.

Progress and Treatment.—On admission the patient was put on a course of penicillin (200,000 units four-hourly) and sulphadimidine (sulphamezathine) (six tablets in the first hour, three four-hourly for 24 hours, and then two four-hourly to a total of 40 g.). Abdominal pain and tenderness, drowsiness, and pyrexia persisted. Faeces were reported as positive for *Salm. paratyphi B* phage type Taunton. Serum gave a positive agglutination with this organism to a titre of 1 in 250 (H). On the 14th day of disease a course of chloramphenicol was begun (2 g. in first hour, 0.5 g. four-hourly for five days, and then 0.25 g. four-hourly for four days—a total of 23 g. in nine days). Within 24 hours there was a change in the patient's condition. She was brighter and said she felt much better. This was in marked contrast to her previous outlook. The abdominal tenderness improved, disappearing after three days. Her temperature was normal on the fourth day (Chart 3). Faeces were still positive for *Salm. paratyphi B* on the fifth day of treatment, but negative thereafter. *In vitro* tests showed that the infecting organism (*Salm. paratyphi B* phage type Taunton) was sensitive to chloramphenicol.

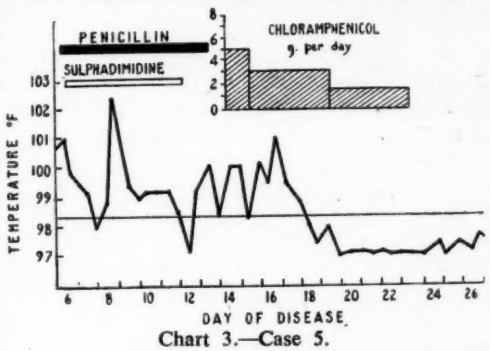


Chart 3.—Case 5.

Case 6

A boy aged 12 was admitted on September 19, 1949, with a history of headache, abdominal pain, pyrexia, and constipation for four days.

On examination the abdomen was moderately distended. The tip of the spleen was palpable. Rose-coloured spots were present on the abdomen and legs; there was slight generalized adenitis; and the tongue was furred. His temperature was 99.8° F. (37.1° C.) and pulse 94.

Progress and Treatment.—Cultures of blood and faeces were positive for *Salm. paratyphi* phage type 3A. Serum gave a positive agglutination with this organism to a titre of 1 in 250 (H). Chloramphenicol was begun on the seventh day of illness (2 g. in first hour, 0.5 g. four-hourly for five days, and then 0.25 g. four-hourly for four days—a total of 23 g. in nine days). There was a dramatic change in the patient's condition. Within 24 hours he no longer complained of headache or abdominal pain. His temperature became normal in 18 hours and, apart from a slight rise (99° F., or 37.2° C.) on the fifth day, remained normal. Faeces were negative for *Salm. paratyphi* on the fifth day. Four subsequent specimens were also negative.

Carriers

During July three apparently healthy faecal carriers of *Salm. paratyphi B* phage type 3A were admitted and treated with chloramphenicol. The dosage given was 16.5 g. in seven days (0.5 g. four-hourly for four days, and then 0.25 g. four-hourly for three days). This dosage had no effect on the carrier state.

Comment

The satisfactory evaluation of the effect of chloramphenicol is not possible in so small a series of cases, especially in the absence of a control group. The rapid improvement and clinical recovery which coincided with treatment, however, were most impressive. This was particularly so in those treated early in the disease.

The dosage of chloramphenicol adequate to produce a well-marked clinical response did not in all cases render the faeces free from the infecting organisms. A similar observation was made in the case of typhoid fever by Woodward *et al.* (1949) and by Rumball and Moore (1949).

In vitro tests showed that both *Salm. paratyphi B* phage type 3A, and *Salm. paratyphi B* phage type Taunton were sensitive to chloramphenicol. It was encouraging to note that in a case in which sensitivity tests were carried out after treatment the organism had not become resistant to chloramphenicol.

It remains to be seen whether larger doses over longer periods will prevent the development of the convalescent carrier state, and whether the drug is effective in treatment of the chronic carrier condition.

I am indebted to Dr. J. Grant, medical superintendent, for his invaluable advice in the preparation of this paper, and to Dr. R. Norton, Director of the M.R.C. Public Health Laboratory, Blakelaw, Newcastle-upon-Tyne, who carried out all bacteriological investigations, including the chloramphenicol sensitivity tests.

REFERENCES

Christie, A. B. (1949). *Post-Grad. med. J.*, **25**, 409.
Kiledjian, Y. (1949). *Lancet*, **2**, 629.
Montuschi, E. (1949). Ibid., **2**, 675.
Rumball, C. A., and Moore, L. G. (1949). *Brit. med. J.*, **1**, 943.
Woodward, T. E., *et al.* (1948). *Ann. intern. Med.*, **29**, 131.

DIFFRACTION METHODS OF MEASURING RED CELL DIAMETERS

THEIR USE IN CLINICAL HAEMATOLOGY*

BY

ALAN J. HIRD, M.B., Ch.B., B.Sc., M.R.C.P.

(From the Gardiner Institute of Medicine, University of Glasgow)

An important feature of many anaemias is the alteration which occurs in the size of the average red cell. This alteration is important in diagnosis and in treatment, since, for example, many anaemias associated with increased red cell size have a common aetiological basis and respond to liver therapy.

The recognition of changes in red cell size can be made in various ways. Probably the oldest is direct inspection of blood films, stained or unstained, under the microscope—a method fraught with difficulty even for those accustomed to making blood examinations and with positive danger for those not so accustomed. Actual measurement of the diameters of a large number of cells (Price-Jones, 1929) converts the method into one of considerable accuracy but of such tediousness that it is ruled out except for special research. An entirely different method, depending upon measurements of the packed cell volume and of the red cell count, gives a value for the mean corpuscular volume (Wintrobe, 1946). While the packed red cell volume can be determined with an accuracy of ±1%, the red cell count (and consequently the mean corpuscular volume) is subject to errors of at least ±5%.

An ingenious alternative method for measuring the mean diameter of red cells depends upon the diffraction of light around the edges of the cells in an unstained film in a manner similar to that which occurs in a diffraction grating. By suitable optical methods the diffracted light can be projected upon a ground-glass screen as a series of coloured haloes (when ordinary white light is used). The diameter of the haloes varies inversely with the average diameter of the red cells. This method was originally described by Pijper (1919), and a later article (Pijper, 1947) gives a full historical review, including references to modifications by other workers, together with a detailed account of the technique and its application. It is claimed not only that the mean cell diameter can be determined but also that the degree of anisocytosis can be estimated by the degree of spread between the inner violet and outer red rings. Brief descriptions of the method will also be found in the standard textbooks on haematology (Whitby and Britton, 1939; Todd and Sanford, 1943; Wintrobe, 1946). Some workers have cast doubt upon the accuracy of claims made for diffraction methods (e.g., Fullerton *et al.*, 1933), and the general impression derived from a study of the literature is that the method is a useful confirmatory one but not reliable enough to be of use as a single critical method of diagnosis. A modification of the method, using two lamps (Pryce, 1929), has simplicity to commend it, but has been criticized by Pijper on the ground that it does not measure the diameter of the average cell but that of the smallest cell present in any considerable number.

Objects and Methods of Present Investigation

The object of this investigation was to determine whether the simple diffraction method of measuring the mean red cell diameter was of value in addition to or in place of more elaborate studies. Several uses were considered: (1) as a "screening" device in the diagnosis of untreated cases of anaemia; (2) as a control in the treatment of cases of pernicious anaemia; and (3) in the investigation of certain other conditions, particularly liver disease.

The study covers a period of almost two years, during which time all new cases showing features of haematological interest in one medical unit were personally investigated, and many followed up at intervals. In addition to conditions usually grouped under the heading of primary blood diseases a considerable number of disorders primarily involving other systems were also dealt with. Excluding a large number of investigations in which the diffraction method was used but for various reasons a complete blood examination was not made, there remain 353 blood examinations on 205 individuals in which haemoglobin, red and white cell counts, haematocrit, absolute values, sedimentation rate, and icterus index were determined in addition to the measurement of the mean cell diameter by the diffraction method and examination of stained films. Table I shows the numbers of each type of disease investigated.

Blood in all cases was withdrawn from a vein into a small bottle containing the appropriate amount of oxalate mixture (Wintrobe. 1946). Haemoglobin was determined by the oxyhaemoglobin method (Bell *et al*, 1945), using a

*The proofs of this article were passed by Dr. Hird shortly before his tragic death on December 11, 1949.

TABLE I.—*Diagnosis of 205 Cases Studied (In Order of Frequency)*

Diagnosis	No.	Diagnosis	No.
Pernicious anaemia	34	Bronchiectasis	4
Hypochromic anaemia	27	Steatorrhoea	
Normal	16	Infectious mononucleosis	
Chronic lymphatic leukaemia	8	Chronic myeloid leukaemia	
Acute hepatitis	9	Cardiac failure	
Bronchial carcinoma	7	Lymphadenoma	
Lead-poisoning	6	Myelomatosis	
Purpura, Chronic renal failure, Cirrhosis of liver	5	Haematemesis and melaena	3
		Gastric carcinoma	
		Banti's syndrome	
		Myxoedema	
		Miscellaneous	46

"Spekker" photo-electric absorptiometer; red and white cell counts were made with the same pipettes, counting-chamber, and cover-glass throughout the entire period, and packed cell volumes were measured by Wintrobe's method. Mean red cell diameters were measured on a "blood cell tester" of Pijper's (1935) design manufactured by Zeiss, the diameter of the yellow ring being used and the conversion table constructed by Pijper (1947) employed to express the value in μ.

In addition, 100 films were also measured by the two-lamp method, which was chosen on account of the extreme simplicity of the apparatus required. Little difficulty was experienced in obtaining consistent readings in films with pronounced macrocytosis, since in them the haloes were small and correspondingly bright: in some films with microcytosis, on the other hand, the colours, being spread out over a wider area, were lessened in intensity, and it was much more difficult to make measurements that could be duplicated. The Pijper apparatus can be read in an ordinarily illuminated room provided that the ground-glass screen is shielded from direct light, but the two-lamp method requires a practically darkened room and a considerable space in which to carry it out. The use of oxalated blood, the delay (never more than one hour) between the withdrawal of blood and the making of films, and the thickness of the film (provided that haloes could be elicited at all) appeared to have little effect on the reading by either method.

Results

Comparison of Pijper's Instrument with the Two-lamp Method of Merlin Pryce.—One hundred consecutive films were read by the two methods, both yellow and red rings being measured in Pijper's instrument, since the two-lamp method depends upon the position of the latter ring. The average mean cell diameter by the two-lamp method was almost exactly 1 μ less than by Pijper's method using the yellow ring (6.91 compared with 7.89) and 0.5 μ less when the red ring was used. There was moderately good correlation between individual readings.

Relation of Mean Cell Diameter to Mean Corpuscular Volume.—The mean cell diameters for the 353 observations were plotted against the mean corpuscular volumes obtained from the red cell count and the haematocrit (Fig. 1). As will be seen, there is a general correlation between the two values, but the degree of scatter is disappointingly wide—e.g., a mean cell diameter of 7.5 μ by the diffraction method was obtained with bloods in which the mean corpuscular volume varied between 58 and 98 c.μ (with an isolated figure of 116). Part of this error is likely to be due to the error in determining the red count, but the discrepancies are greater than can be explained solely on this basis. As a method of estimating macrocytosis (in the sense of increased corpuscular volume), therefore, the mean cell diameter as determined by diffraction methods must be considered unreliable except in the extreme upper range (>8.5 μ), being subject to errors of both commission and omission, while in assessing microcytosis it seems to be valueless, although, unfortunately, no cases showing microspherocytes were encountered in this series.

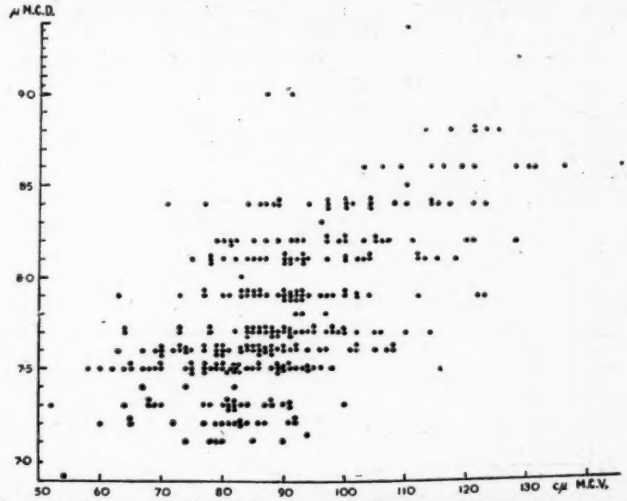


FIG. 1.—Mean cell diameters as determined by Pijper's instrument plotted against mean corpuscular volumes (353 observations).

Use as a Screening Examination in the Investigation of Untreated Cases of Anaemia.—Here the principal, if not the sole, interest centres upon cases showing a high mean cell diameter. Taking the figure of 8 μ as a dividing-line, there were 108 examinations in which a higher value was obtained. Fifty-five occurred in patients with pernicious anaemia or steatorrhoea (including some under treatment), 23 in liver disease, and 30 in miscellaneous conditions. No normal subject was found to have a mean cell diameter greater than 8 μ. There were 11 individuals in whom the value was higher than 8.5 μ, and 9 of these were patients with pernicious anaemia or steatorrhoea, untreated or in relapse. It is of interest that 18 cases of pernicious anaemia or steatorrhoea seen before treatment or in a state of relapse all showed a mean cell diameter of more than 8 μ. In some of these the anaemia was not severe (in one case which presented with subacute combined degeneration of the cord the haemoglobin was 13.9 g. %). It seems improbable, therefore, that an untreated case of pernicious anaemia will be missed by diffraction methods of estimating the mean cell diameter, but the exact diagnosis and the distinction from other causes of a high cell diameter depend of course upon fuller blood examination. Fig. 2 shows the distribution of conditions showing a mean cell diameter greater than 8 μ at the initial examination (excluding patients with pernicious anaemia first seen while under treatment).

Use in Control of Treatment in Pernicious Anaemia.—Fig. 3 (average of 8 cases) shows the return to normal of mean corpuscular volume and mean cell diameter under specific therapy. The fall in mean cell diameter roughly

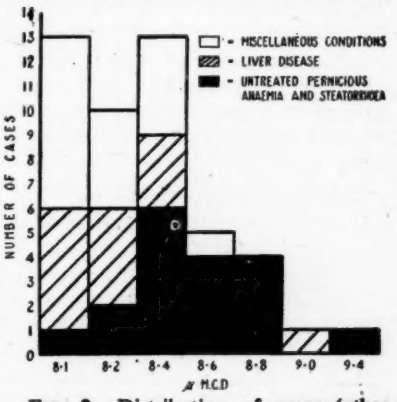


FIG. 2.—Distribution of cases (other than pernicious anaemia under treatment), showing a mean cell diameter greater than 8 μ. The variations in the scale for the mean cell diameter are due to the effect of the conversion table, which does not include certain intermediate values.

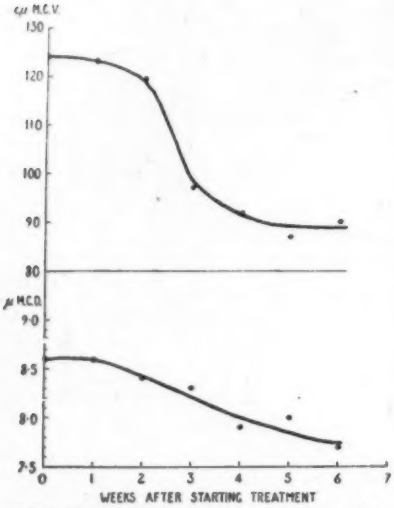


FIG. 3.—Return of mean corpuscular volume and mean cell diameter to normal in pernicious anaemia under specific therapy (average for eight cases).

parallels the decrease in macrocytosis but takes somewhat longer to return to normal levels. Of 25 cases of pernicious anaemia or steatorrhoea followed up as out-patients and about which sufficient data have accumulated, 17 have consistently displayed a mean cell diameter of less than 8 μ, and of these only one has been regarded as not being satisfactorily controlled by treatment. This patient, suffering from steatorrhoea, has shown a haemoglobin of around 10–12 g. % over long periods with, usually, a hypochromic picture, which has responded poorly to oral iron and not at all to increased dosage of liver or to administration of folic acid. Five patients have shown a mean cell diameter of more than 8 μ on one or two occasions, while symptomless and with otherwise normal blood findings. Three have shown a mean cell diameter fairly consistently above 8 μ. One was a woman of 68 years with a severe uterine prolapse for which no radical treatment was possible and which was associated with recurrent cystitis. Despite heavy dosage of liver preparations, haemoglobin averaged 10–11 g. % and macrocytosis persisted. Two other patients, both male, have enjoyed excellent health, with no neurological complications, and shown normal haemoglobin values, but have had persistent macrocytosis (confirmed by mean corpuscular volume determination) despite increases in dosage of liver. It can probably be said that most properly treated patients with pernicious anaemia will show a mean cell diameter of less than 8 μ; while a value higher than this should suggest the need for further investigation but is not by itself necessarily an indication of inadequate treatment.

Use in Other Conditions Showing a High Mean Cell Diameter.—These included a wide variety of diseases (Table II), but the most notable group was that of diseases involving the liver as shown in Table III. It is of interest that in only two of these 18 cases was the mean corpuscular volume greater than 100 c.μ. One case with cirrhosis and one with Banti's syndrome showed a persistently high cell diameter despite the presence of a severe hypochromic microcytic anaemia resulting from oesophageal bleeding.

The degree of spreading of the haloes was determined by measuring the diameters of the red and violet rings in 14 films from patients with liver disease and 12 from patients with pernicious anaemia in relapse, in all of which the mean diameter was greater than 8 μ. The results shown in Table IV, demonstrate no appreciable difference in the degree of anisocytosis in the two conditions. This finding is not in accord with the results of inspection of the films. The red cells in liver disease showed anisocytosis little greater than normal, certainly nothing like that seen in pernicious anaemia, nor was there greater rouleaux formation than normal in the thin parts of the film which were used in the diffraction method. It seems that diffraction methods by themselves are unable to differentiate between the macrocytosis of pernicious anaemia and that of liver disease, and the claim that separation of the rings in the halo represents anisocytosis seems debatable. It is hoped to make this macrocytosis of liver disease the subject of a further study

TABLE II.—*Diagnosis in All Cases Showing a Mean Cell Diameter Greater than 8 μ on One or More Occasions*

Condition	No.	Condition	No.
Liver disease	13	Cardiac failure Chronic lymphatic leukaemia Dermatomyositis Hypochromic microcytic anaemia Lead-poisoning Lympho-epithelioma Refractory anaemia	1
Carcinoma of colon Chronic renal failure Lymphadenoma Myeloma ..	2		
Aplastic anaemia Bronchial carcinoma ..	1		

TABLE III.—*Mean Cell Diameters in Cases of Liver Disease (Initial Findings in Each)*

Condition	No. of Cases, with M.C.D.		Total
	>8 μ	<8 μ	
Acute hepatitis	7	2	9
Cirrhosis	4	1	5
Banti's syndrome	1	2	3
Obstructive jaundice	1	—	1
Total	13	5	18

TABLE IV.—*Mean Cell Diameter and Degree of Variation in Liver Disease and Pernicious Anaemia*

Condition	M.C.D. (μ)	Range (μ)
Liver disease	8·38	7·80–9·09 (−0·58 to +0·71)
Pernicious anaemia	8·56	8·00–9·33 (−0·56 to +0·77)

Conclusions

The measurement of the mean red cell diameter by diffraction methods, as an alternative to the determination of the mean corpuscular volume, cannot be recommended, since the relationship between the two is not close enough.

The finding of a mean cell diameter greater than 8 μ by Pijper's instrument (using the yellow ring) will lead to detection of the great majority of cases of pernicious anaemia, either untreated or in relapse, but a number of other haematological conditions will also be included, of which the most strikingly consistent group is that associated with liver disease.

In the control of treatment of pernicious anaemia the presence of a normal mean cell diameter (<8 μ) suggests that treatment is reasonably adequate, but the satisfactory response to treatment of the majority of patients in this small series makes this difficult to assess. On the other hand, the finding of a mean cell diameter greater than 8 μ, even repeatedly, does not necessarily imply inadequate therapy.

Some doubt is cast upon the ability of the method to estimate the degree of anisocytosis.

Summary

The use of diffraction methods of measuring mean red cell diameters is described and their value in routine blood examination discussed. They are of value as a "screening" examination, particularly in detecting untreated cases of pernicious anaemia, but fuller blood examination is required for an exact diagnosis. In following up cases of pernicious anaemia under treatment these methods are of value, in conjunction with other blood findings, but moderately abnormal findings do not always imply an unsatisfactory clinical or haematological state. Liver disease

is often associated with a high mean cell diameter as shown by these methods, a result which may not be arrived at by other means.

My thanks are due to Professor J. W. McNee for advice and criticism in the preparation of this paper.

REFERENCES

Bell, G. H., Chambers, J. W., and Waddell, M. B. R. (1945). *Biochem. J.*, **39**, 60.
Fullerton, H. W., Lyall, A., and Davidson, L. S. P. (1933). *Quart. J. Med.*, n.s. **2**, 561.
Pijper, A. (1919). *Med. J. S. Afr.*, **14**, 472.
— (1935). *Lancet*, **1**, 1152.
— (1947). *J. Lab. clin. Med.*, **32**, 857.
Price-Jones, C. (1929). *J. Path. Bact.*, **32**, 479.
Pryce, D. M. (1929). *Lancet*, **2**, 275.
Todd, J. C., and Sanford, A. H. (1943). *Clinical Diagnosis*, 10th ed., p. 232. Saunders, Philadelphia.
Whitby, L. E. H., and Britton, C. J. C. (1939). *Disorders of the Blood*, 3rd ed., p. 545. Churchill, London.
Wintrobe, M. M. (1946). *Clinical Haematology*, 2nd ed., pp. 239, 264. Kimpton, London.

TWO SUCCESSFUL RESECTIONS FOR CARCINOMA OF PANCREAS

BY

HAROLD DODD, Ch.M., F.R.C.S.

Surgeon to King George Hospital, Ilford; the Royal Hospital, Richmond; the Royal London Homoeopathic Hospital; and the Princess Louise Hospital for Children, Kensington

Two cases of carcinoma of the pancreas in which a resection operation was carried out successfully are described below. The first patient recovered from the operation, gaining 5 lb. (2.27 kg.) in weight, but died five months later from recurrences in the abdomen. The second patient was alive and well when seen 12 months after her operation; she had put on weight, and was able to do her work as a housewife. Up to that date there was no sign of recurrence. The procedure included excision of the caecum, ascending colon, and right transverse colon.

So far no record of a colon excision with the pancreas has been traced in the literature. Hunt (1941) exhaustively reviews all cases of carcinoma of the ampulla of Vater up to that date, and includes synoptic tables showing the type of operation and the results achieved. Cattell (1948) goes more fully into technique, and Brunschwig (1942) reviews the different operative treatments but makes no mention of the colon.

Case 1

A man aged 55 was first seen in October, 1947, when he complained of jaundice of four months' duration. He gave a history of general lassitude, breathlessness, dizziness on exertion, and loss of weight for two years; he said that in the last five months he had lost 19 lb. (8.62 kg.). For 30 years he had had intermittent epigastric pain two hours after a meal, and this was relieved by taking more food and by alcohol. He had had the usual infectious diseases of childhood and also occasional attacks of influenza. In 1917, in Italy, he had had an attack of dysentery, and in 1922 appendicitis, which was treated medically. His mother had died of pulmonary tuberculosis, and his father, at 76 years of age, of heart disease.

On examination he was seen to be a thin spare man, deeply jaundiced. The liver was palpable ½ in. (1.25 cm.) below the costal margin, and the gall-bladder was felt to extend from the ninth costal cartilage to the right iliac fossa. On October 30 he was admitted to a medical ward with a tentative diagnosis of carcinoma of the head of the pancreas.

Operation, November 4.—On opening the abdomen under local analgesia supplemented with open ether (Dr. Goldman) the gall-bladder was seen to be distended to the caecum and there was the scar of a healed duodenal ulcer. The liver was normal in size and consistency, as were also the abdominal viscera. The pancreas was of hard consistency throughout; around the entrance of the common bile duct there was a stony-hard portion which, by inserting the blunt end of a straight needle, was proved to be composed of tissue and not a stone in the common bile duct. A diagnosis was made of carcinoma of the head of the pancreas around the entrance of the ducts into the duodenum. It was considered that a resection of it was possible.

Procedure.—The duodenum was mobilized from the posterior abdominal wall and the head of the pancreas exposed from behind, where a firm irregular mass the size of an almond was present around the opening of the ducts. The stomach was divided above the pyloric antrum. The common bile duct was ligated with stout thread and sewn over, and the duodenum was mobilized to 1 in. (2.5 cm.) beyond the duodeno-jejunal flexure. The pancreas was divided at the junction of its distal and middle thirds; its duct was found to be distended to a size rather larger than that of the ureter. The first 6 in. (15 cm.) of the jejunum was easily drawn up through the mesocolon, which was closed snugly round it. The neck of the gall-bladder was anastomosed to the distal end of the jejunum. The end of the pancreatic duct was anastomosed to the side of the jejunum about 2 in. (5 cm.) distal to the first anastomosis, where the two were easily approximated. The end of the stomach was anastomosed to the side of the jejunum, immediately below the pancreas. A soft rubber drain was passed to these anastomoses and the wound was closed.

Examination of sections of the hard mass around the common bile duct confirmed the clinical diagnosis of carcinoma of the head of the pancreas. The tumour was infiltrated by large anaplastic epithelial cells with pronounced hyperchromatosis and mitosis. Differentiation to glandular structure was seen in parts of the growth. Extensive lymphoid-cell infiltration was also present.

On January 16, 1948, the patient weighed 9 st. 3 lb. (58.51 kg.)—an increase of 5 lb. (2.27 kg.). By February 13 he was again jaundiced, and a recurrence was palpable in the scar of the abdominal incision. He died in April of asthenia.

Comment.—In this case the common bile duct was so large that its anastomosis to the jejunum would have been practicable, and I think this would have been a sounder operation. The patient had been jaundiced for four months when he was first seen, and I make a plea that in cases in which painless jaundice has been present for a month the possibility of carcinoma of the pancreas should be considered and a surgical opinion sought. The mortality of laparotomy is probably 1 to 2%; that following observation of carcinoma of the bile ducts or pancreas is 100%. Some 80% of the patients will recover after resection of the pancreas.

Case 2

A married woman aged 43 was first seen in September, 1948, when she complained of a symptomless lump in the right side of the abdomen, which she had first noted two and a half years before but which had enlarged in the last seven weeks. She had some flatulence and nausea, but no pain or vomiting. Recently her appetite had been poor. She weighed 7 st. 6 lb. (47.17 kg.), but her weight had never been more than 8 st. (50.8 kg.).

On examination a tense cystic, smooth globular swelling the size of a child's head was found on the right side of the abdomen (Fig. 1*a*). The tumour was movable from left to right but not up and down; on pressure it flattened into the loin, but reappeared on coughing; it did not move on respiration. The liver, gall-bladder, kidneys, and spleen could not be felt. On rectal examination the pelvis was found to be clear. Provisionally the diagnosis rested between (1) mobile retroperitoneal sarcoma in the area of the pancreas, duodenum, and transverse mesocolon; (2) an atypical carcinoma of the pancreas; and (3) an atypical pelvic tumour rising into the abdomen.

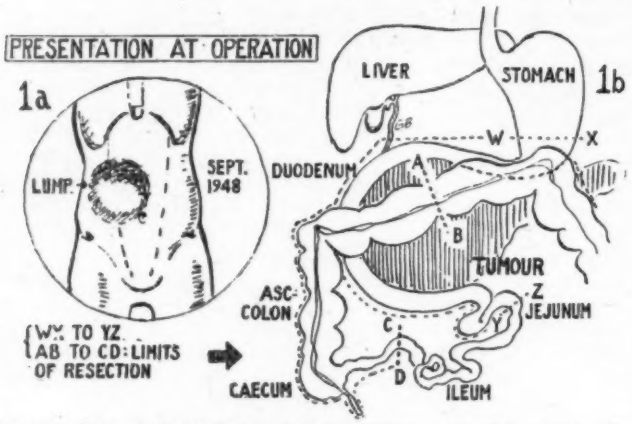


FIG. 1.—Case 2 (*a*) The site of the tumour. (*b*) The tumour as presenting at operation.

Examination of the blood showed: haemoglobin, 42%; red blood cells, 2,600.000 per c.mm.; leucocytes, 10,300 per c.mm. (polymorphonuclears 84%, lymphocytes 16%); blood urea concentration, 34%. A catheter specimen of urine yielded a negative quantitative result, both regarding the deposit and on culture.

Operation.—On October 12 an extended right paramedian incision was made under thiopentone and open ether anaesthesia (Dr. Badock), supplemented by local infiltration of the abdominal wall and splanchnic ganglia with 1 in 1,000 amethocaine hydrochloride. A large vascular, apparently cystic tumour somewhat smaller than an adult head was found lying within the curvature of the duodenum, which was stretched like a strap over it superiorly and laterally. It was adherent to the stomach, duodenum, pancreas, ascending colon, and transverse colon, and bulged through the stretched right mesocolon. The gall-bladder and liver were normal. The swelling was aspirated, but nothing was withdrawn (Fig. 1*b*).

Procedure.—An attempt to shell out the swelling through the mesocolon was abandoned because of copious bleeding and because no plane of cleavage was found. At this stage it was decided that the tumour arose from the pancreas and that its excision was possible and necessary. The colon and duodenum were mobilized from the flank into the wound and the tumour was brought forward with the duodenum stretched tightly over it. The common bile duct and the gastro-duodenal artery were divided between ligatures. The stomach was sectioned above the pyloric antrum. The duodenum was mobilized to the first inch of the jejunum, where it was incised. The mass was brought out of the abdomen attached to the descending and transverse colon and the pancreas; the latter was cut at the junction of the left and middle thirds, well removed from the swelling (Fig. 2). The tumour was so intimately associated with the right colic artery and mesocolon that there was danger, if they were separated, of disseminating the growth and of imperilling the blood supply of the colon; therefore the ileum was sectioned and the transverse colon was transected at its middle. The tumour, with the pyloric antrum, the duodenum and first inch of the jejunum, the last 6 in. (15 cm.) of the ileum, the caecum, ascending colon, hepatic flexure, and right half of the transverse colon, was removed.

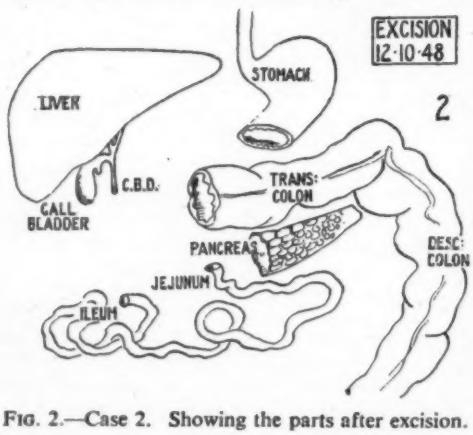


FIG. 2.—Case 2. Showing the parts after excision.

The Reconstruction.—The first 6 in. of the jejunum was drawn through the transverse mesocolon, and the opening in the latter was closed and sutured to it (Fig. 3). The common bile duct was anastomosed to the centre of the end of the jejunum; as it was not dilated, this was difficult. (In dealing with a similar case in future I intend to use the gall-bladder instead.) The pancreatic duct was not dilated, and was considered too small to connect to the jejunal mucous membrane. The end of the pancreas was oversewn and the stump was implanted into the side of the jejunum, the sero-muscular wall being incised to receive it. The stomach was anastomosed end to side to the jejunum. The ileum was united end to end to the transverse colon. This last step constituted a weak link in the chain, but, thanks to the use of penicillin and "sulphatriad" (sulphathiazole, sulphadiazine, and sulphamerazine), combined with plasma and blood transfusion, all was well. The abdomen was closed with nylon sutures, and drainage-tubes were inserted to the anastomoses.

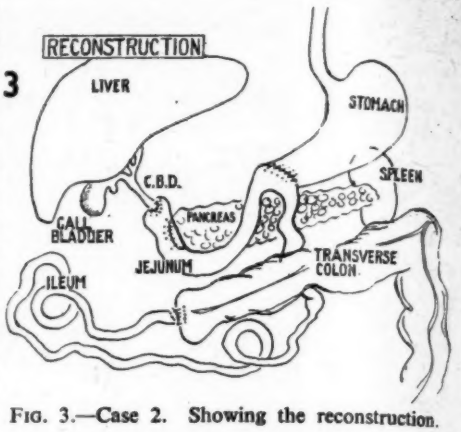


FIG. 3.—Case 2. Showing the reconstruction.

Pathological Report (*Dr. Cuthbert Dukes*).—The specimen consisted of a large oval tumour measuring 5 by 4 in. (12.5 by 10 cm.) and occupying the region of the pancreas. The growth was surrounded by the duodenum, all of which was removed with the operation specimen. The caecum and a portion of the transverse colon were also removed. Microscopical examination showed the tumour to be composed of fusiform epithelial cells arranged in small clumps and distributed irregularly. The histological appearances were those of an anaplastic carcinoma of the body or the tail end of the pancreas. Judged from its histology the growth was probably of a high grade of malignancy.

The patient was given infusions of salt, sugar, and water, and transfusions of plasma and blood, under the direction of Dr. Sterndale Bennett. The post-operative course was uneventful, except for a small discharge of bile for six days, beginning on the fifth day.

The following post-operative results of tests of blood, urine, and faeces were obtained by Dr. John Spencer.

October 18.—Catheter specimen of urine: occasional red blood cells in deposit; culture demonstrated presence of coliform organisms; total chlorides, 6 g. per litre. Blood: haemoglobin, 85%; red cells, 4,350,000 per c.mm.; blood urea, 35 mg. per 100 ml.; plasma proteins, 7.5 g. per 100 ml.

October 19.—Blood: haemoglobin, 90%; red cells, 4,820,000 per c.mm., blood urea, 24 mg. per 100 ml.; resting blood sugar, 160 mg. per 100 ml.

November 5.—Fasting blood sugar, 120 mg. per 100 ml. Thirty minutes after the administration of 50 g. of glucose the blood sugar was 120 mg. per 100 ml., one hour after the glucose was given the reading was 121 mg., and within another 30 minutes the level had fallen to 100 mg. per 100 ml. No sugar was found in the urine. Examination of the faeces gave the following percentage figures: total fat, 7.32; unsplit neutral fat 1.52; split fat 5.8. It was concluded that the fat-splitting mechanism was functioning adequately.

May 30, 1949.—Blood, normal; blood sugar, normal; faeces, fat-splitting mechanism normal; urine, normal. The patient was well in all respects and maintaining her weight and strength.

In December, 1949, the patient was well and was doing her work as a housewife without sign of recurrence.

Comment.—The magnitude of this operation was increased by the resection of the ascending and the transverse colon—a procedure which seems not to have been called for hitherto, as no record of such a step has been found in the literature.

I gladly acknowledge my indebtedness to Drs. Sterndale Bennett, Bentley, and John Spencer (of the King George Hospital, Ilford) for their help with this patient.

REFERENCES

Brunschwig, A. (1942). *Surgery of Pancreatic Tumours.* St. Louis.
Cattell, R. B. (1948). *Surg. Clin. N. Amer.*, **28**, 761.
Hunt, V. C. (1941). *Ann. Surg.*, **114**, 570.

Medical Memoranda

Hernia through Foramen of Winslow

The following case was complicated by the fact that the herniated loop had re-entered the general peritoneal cavity through the lesser omentum.

CASE REPORT

A woman aged 41 was admitted to hospital complaining of severe abdominal pain which had come on some 20 hours previously. The onset had been sudden, and the pain had increased in severity, especially in the upper abdomen. Some seven hours after the onset she had vomited, and this had recurred about six times since. The bowels had not moved, nor had she passed flatus since the pain started. She had no other symptoms and the last menstrual period had been two weeks before. On specific interrogation she admitted to a vague type of indigestion which "came on before supper if I had a fatty dinner." The previous history was otherwise entirely negative.

Examination showed her to be a well-nourished woman, and in obvious pain. Her temperature was normal. There was a fine whitish fur on the tongue, and the breath was slightly fetid. The abdomen did not move on respiration, and tenderness and guarding were present all over, but more pronounced in the epigastrium. There was loss of liver dullness in front but not in the axillary line. Rectal examination revealed a rather bulky uterus but no other abnormality. No abnormal signs were found in the other systems except rather frequent extrasystoles. The pulse rate was 92 and the blood pressure 135/85. As she did not vomit after admission the character of the vomitus was not ascertained.

A tentative diagnosis of perforated peptic ulcer was made and a laparotomy performed. In all fairness to those who saw the patient I must record that this diagnosis was made with some trepidation. There were many features which did not fit in—e.g., the ingravescent nature of the pain and the absence of frank rigidity. It was also difficult to reconcile a perforation of 20 hours' duration with her extremely good general condition.

Operation.—Under general anaesthesia a high right paramedian incision was made. On opening the peritoneum the first significant finding was the absence of free fluid; next, the caecum presented in the upper part of the wound, grossly dilated and overlying the liver. This must have been the cause of the loss of liver dullness noted clinically. The findings at laparotomy are shown in Fig. 1. At first this was thought to be a case of volvulus of an abnormally mobile right colon, but on tracing the loop to its base under cover of the liver a fold of peritoneum was found under which the loop had passed. It then seemed that we were dealing with an obstruction by a peritoneal band, and the obvious treatment would be to divide it and thus free the imprisoned gut (Fig. 2).

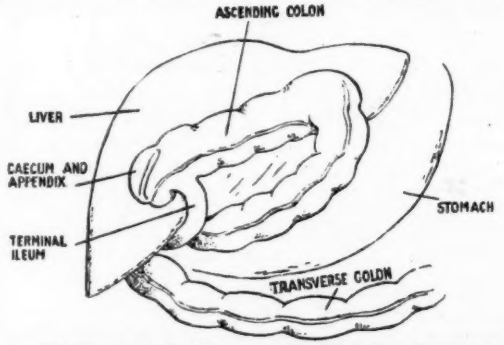


FIG. 1.—Diagram of findings at laparotomy. Terminal ileum, caecum, ascending colon, and part of transverse colon were lying superficially, forming a loop the base of which disappeared under the liver margin.

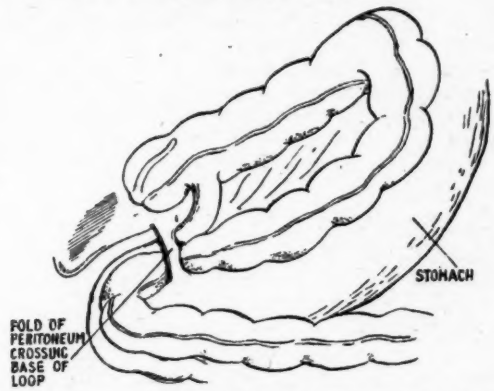


FIG. 2.—Diagram of findings after the liver had been turned up. The band of peritoneum shown crossing the base of the loop was the right "free edge" of the lesser omentum.

The true diagnosis was not evident until palpation of the fold revealed forcible pulsation and investigation proved that it contained the hepatic artery, common bile duct, and portal vein, and that it was in fact the right "free edge" of the lesser omentum. The loop of gut had entered the lesser sac through the foramen of Winslow and traversed the gastro-hepatic omentum to reappear in the general peritoneal cavity between the liver and the lesser curve of the stomach.

It was impossible to reduce the hernia by traction, as the loop was so distended and the hiatus so small. Enterotomy was also in vain, and it was decided to resect the offending loop. This was considered feasible in view of the excellent condition of the patient under the anaesthetic; also, the length of mesentery was such as to render the procedure relatively simple. Resection of the loop was accordingly effected and an ileo-transverse colostomy performed. It was then considered that the patient had had as much manipulation as was desirable and no attempt was made to define the precise peritoneal anomalies or to close the gap between the liver and the stomach.

Apart from some infection of the base of the right lung convalescence was uninterrupted and the patient was discharged well three weeks later.

I am grateful to Mr. J. F. Heslop for permission to publish details of the case. Thanks are also due to Dr. S. Kay for the drawings, and to Mr. C. I. Raeburn for his invaluable assistance in the preparation of the report.

JOSEPH N. LEWIS, M.B., B.Ch.,
Late House-surgeon, Park Hospital, Davyhulme.

Treatment of Megaloblastic Anaemia with Vitamin B_{12}

In view of the interest aroused by the recent isolation of vitamin B_{12} simultaneously by Lester Smith (1948, 1949) in Britain and Rickes *et al.* (1948) in the U.S.A., and its action in megaloblastic anaemias (Ungley, 1949), we feel that it would be of interest to record our experience of this substance in the treatment of two cases of pernicious anaemia which were recently under our observation. The amount of substance available to us did not permit treatment to be completed and continued, but a satisfactory and unequivocal initial response was obtained in both cases.

The preparation employed was made by Glaxo Laboratories from the mould *Streptomyces* and was a clear brown liquid, each 1 ml. containing 10 μg. of vitamin B_{12}.

CASE 1

A housewife aged 65 was admitted on September 2, 1949, complaining of increasing lassitude, pallor, and dyspnoea on exertion. Sternal pain radiating down both arms brought on by exercise had also been experienced during the preceding few months. On examination she was found to be rather obese and very pale. There were no detectable abnormalities in the chest, abdomen, or heart, the blood pressure was 150/80, the tongue normal, and oedema was absent; apart from bilateral absence of vibration sense in both legs the central nervous system was normal. An electrocardiogram soon after admission revealed negative T waves in Leads I and II which were ascribed to coronary artery disease. The faecal occult blood was negative.

A blood count the day before admission showed: haemoglobin, 40%; red cells, 1,490,000 per c.mm.; colour index, 1.3; white cells, 5,700 per c.mm. Anisocytosis and poikilocytosis were prominent on examination of the film, and macrocytes were in evidence. The mean corpuscular volume was 143 c.μ, and the concentration method suggested recently by K. S. Rodan showed a few megaloblasts in the peripheral blood.

On September 4, 20 μg. of vitamin B_{12} was injected intramuscularly and no other therapy was permitted. The next day examination of the peripheral blood revealed 2% reticulocytes, and these continued to rise rapidly, reaching a peak of 17% on September 8 (Fig. 1).

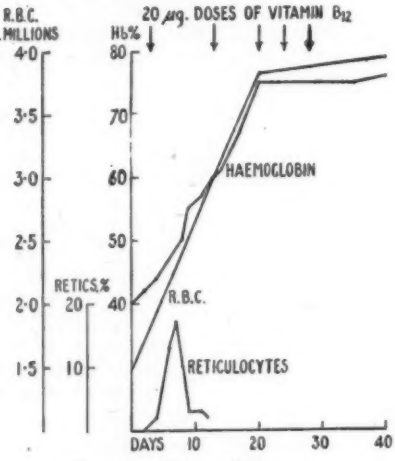


FIG. 1.—Chart of Case 1.

On September 9 the haemoglobin had reached 50%, and by September 14, 60%. Vitamin B_{12}, 20 μg., was administered on September 14, 21, 25, and 29, and on September 21 and 30 the haemoglobin was found to be 75%.

We were impressed by the patient's sense of well-being soon after the first dose, and no ill effects were observed after each injection except that the patient complained of being "drowsy and tired" for a few hours; this effect was thought to be psychogenic. Owing to exhaustion of the supply of vitamin B_{12} an orthodox liver preparation was started on October 8. The total amount of vitamin B_{12} administered was 100 μg.

CASE 2

A woman aged 77 was admitted on August 5, 1949, complaining of increasing weakness, pallor, dyspnoea on exertion, and persistent anorexia. These symptoms had gradually developed over a period of two years, but had become very much worse lately. For a few weeks before admission she had been much troubled by vomiting, and loss of weight had been severe.

On examination the patient was found to be very pale and looked ill. The tongue was smooth and she appeared to have lost a considerable amount of weight. There were no detectable abnormalities in the heart or abdomen, but rales were heard at both lung bases. The blood pressure was 150/90, and the central nervous system showed no evidence of subacute combined degeneration. At that time she was thought to have a carcinoma of the stomach, but a barium meal *x*-ray examination on August 12 showed no stomach-filling defect, although a hiatus hernia was revealed.

A histamine test meal revealed no free acid, and a blood count on August 9 showed: haemoglobin, 40%; red cells, 1,400,000 per c.mm.; white cells, 2,000 per c.mm., colour index 1.4. Marked anisocytosis and poikilocytosis were present in the blood film and macrocytes predominated. On August 22 a sternal puncture revealed a megaloblastic marrow, thus clinching the diagnosis of Addisonian anaemia. The faeces were negative for occult blood.

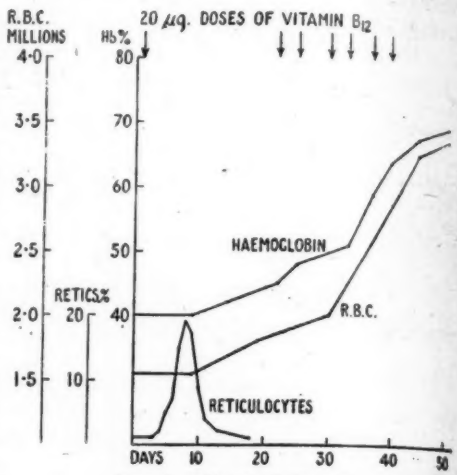


FIG. 2.—Chart of Case 2.

Vitamin B_{12}, 20 μg., was administered intramuscularly on August 23 (no other therapy being permitted) and daily reticulocyte counts were made. These were 1% until August 26, when 2% were detected in the peripheral blood. On the 27th the figure had risen to 5% and a peak of 19% was reached on the 30th (Fig. 2).

The haemoglobin was still 40% on August 31, but this now started to rise, although slower than we expected; on September 12 it was found to be only 45%, and in view of what was considered to be an unsatisfactory haemoglobin response a further injection of 20 μg. of vitamin B_{12} was given that day and a similar amount on September 15, 20, 23, 27, and 30—i.e., 20 μg. twice weekly. The total amount of vitamin B_{12} administered in this case was 140 μg.

By September 30 the haemoglobin had risen to 64%, and was 70% on October 11, but in view of the lack of a further supply of vitamin B_{12} an orthodox liver preparation was substituted, the first dose being given on October 11.

In this case, although the rise in haemoglobin was slow, the rapid general improvement was striking. Within two days of the first injection of 20 μg. of vitamin B_{12} vomiting, which had been troublesome, completely ceased, appetite returned, and the patient showed an active interest in her surroundings; this had previously been lacking.

Conclusion.—It seems that vitamin B_{12} prepared from *Streptomyces* is a potent therapeutic agent in megaloblastic anaemia.

We wish to thank Dr. E. Noble Chamberlain for his encouragement and advice, and Messrs. Glaxo Laboratories Ltd. for the supply of vitamin B_{12}.

C. M. MILLER, M.D., M.R.C.P.,
Visiting Physician.
E. H. MOORHOUSE, M.R.C.S., L.R.C.P.
Assistant Pathologist, Smithdown Road Hospital, Liverpool.

BIBLIOGRAPHY

Berk, L., Denny-Brown, D., Finland, M., and Castle, W. B. (1948). *New Engl. J. Med.*, **239**, 328.
Hall, B. E., and Campbell, D. C. (1948). *Proc. Mayo Clin.*, **23**, 584, 591.
Piney A., and Barkley, T. Y. (1949). *Lancet*, **1**, 1119.
Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R., and Folkers, K. (1948). *Science*, **108**, 134.
—— —— —— —— —— (1948). Ibid., **108**, 634.
Smith, E. L. (1948). *Nature, Lond.*, **162**, 144.
—— (1949). *British Medical Journal*, **2**, 1367.
Spies, T. D., Stone, R. E., and Aramburu, T. (1948). *Sth. med. J.* **41**, 522.
Ungley, C. C. (1949). *British Medical Journal*, **2**, 1370.

Reviews

THE PROBLEM OF LABORATORY ANIMALS

Manual for Laboratory Work in Mammalian Physiology. By Fred E. d'Amour and Frank R. Blood. (Pp. 50; illustrated. 15s.) Chicago: University of Chicago Press. London: Cambridge University Press. 1949.

This laboratory manual describes 50 experiments that may be carried out by students on the rat. The authors, who are attached to the University of Denver, have experienced difficulty in providing larger mammals for class work and have therefore devised a course in which the rat is exclusively employed. The experiments are well distributed over the various systems, and if carried out conscientiously will provide the student with an admirable training. Some of the experiments, such as those involving cannulating the carótid artery or jugular vein, require a considerable degree of manual dexterity.

The shortage of cats, rabbits, or dogs is not peculiar to the United States; in this country research in mammalian physiology is grievously handicapped because of the inadequate supplies of suitable animals. Although tens of thousands of cats and dogs are destroyed annually the present state of the law apparently prevents any of these animals being made available even for acute experiments conducted throughout under full anaesthesia, at the end of which time the animal is destroyed. It has been suggested that breeding stations should be established to provide experimental animals. It has been reliably estimated that, apart from the capital costs for land and buildings, the cost of producing a one-year-old cat would be of the order of £10 or £15. It is believed that some of those in authority would rather have this indefensible extravagance allowed than antagonize the antivivisectionists by amending the law to permit the use of stray animals.

Work on the mammal is now everywhere reduced to a few demonstrations for medical students and an inadequate course even for students doing honours degrees in physiology. The shortage of experimental animals is bound to have a crippling effect on the progress of experimental physiology in this country. The use of the anaesthetized rat for class work would involve either re-interpretation or amendment of the Vivisection Act. It might be worth while for the Physiological Society to take up the matter officially with the Home Office. Should the rat ever become available for student work in this country, then d'Amour and Blood's *Manual* will provide an invaluable guide.

SAMSON WRIGHT.

GRADING MUSCULAR FUNCTION

Muscles: Testing and Function. By Henry O. Kendall and Florence P. Kendall. (Pp. 278; illustrated. £2 1s.) London: Baillière, Tindall and Cox. 1949.

There is nothing novel in the detailed testing of muscle function. What is new is the wholesome revival of interest in the subject, which has recently found expression in the appearance of several useful manuals and monographs. This book, the latest and most elaborate of them, is written by two physiotherapists who have given many years to the care of children suffering from poliomyelitis. No one who has visited the Children's Hospital at Baltimore can fail to have been impressed by the superb work being done there by Mr. and Mrs. Kendall, and this book gives a complete picture of the painstaking methods of examination on which this work is based. The action of every important muscle that can be demonstrated by clinical examination is shown in a series of remarkable photographs, and there are pictures of a number of important paralyses, contractures, and errors of posture. The text itself is equally informative.

The practical implications of their teaching must be considered, however. The disturbing feature, and it is an important one, of the Kendalls' work is the complexity of their system of grading muscle power. There can be no question that some method of recording the action of individual muscles (or where necessary muscle groups) is essential in the management of lower motor neurone disorders, of which poliomyelitis and nerve injuries are by far the most important. Even under epidemic conditions clinicians must be prepared to work out muscle charts in every case of poliomyelitis, and a chart is equally necessary for the squirming infant as for the co-operative adolescent. But one must choose a system of examination and assessment that does not make impossible demands on the examiner's time, and in which the differences between the various grades of muscle power are not less than the unavoidable errors of examination. These variations may be due to temporary fluctuation in the patient's condition and to slight differences in technique between one trained observer and another.

In Great Britain the 0 to 5 system of recording is becoming generally accepted, and, having had experience of it in some thousands of cases of nerve injury and poliomyelitis, I would not like to assist at the introduction of anything more elaborate. It is true that one often makes use of pluses, minuses, and half values—e.g., 2+, 3−, or 4½. Yet these "accidentals" must never be taken seriously; they are helpful to the individual observer but are not an argument in favour of a more elaborate system of notation. The Kendalls are no doubt well able to use all twelve of their grades of muscle power, but it would hardly be impertinent to ask what proportion of the residents leaving the Children's Hospital at Baltimore subsequently employ their elaborate system, and, if they do use it, with what degree of accuracy.

Another objection to the Kendalls' system is their employment of percentages to express the various grades. It is reasonable to suppose that a muscle graded as 80% is twice as strong as one graded 40%. Yet this is not so. Grading of such accuracy could be done only with elaborate machinery wholly unsuited to the needs of clinical practice.

Provided he is not repelled or led astray by this system of charting, the anatomist, the physiotherapist, and the clinician will find here a book that should be a constant source of profit. It cost 41s. before devaluation; it will cost more now, but it is still worth it

H. J. SEDDON.

FREUD: A FRESH TRANSLATION

Three Essays on the Theory of Sexuality. By Sigmund Freud. Authorized translation by James Strachey. (Pp. 133. 10s. 6d.) London: Imago Publishing Co. 1949.

When *Three Essays* made its first appearance forty years ago it may be said to have rivalled the work of Galileo in the storm of indignation, hostility, and recrimination which it evoked. It is remarkable that in spite of this it has been translated into most languages, and reached a fourth German edition by 1920. The book was the basis of a large part of Freudian teaching, and from its

conclusions, with the doctrines set out in *The Interpretation of Dreams*, there developed the theory and practice of psycho-analysis. Not only this, but the startling conclusions on the theory of sexuality have now become fairly generally accepted. This excellent new English translation is most welcome, for if the Freudian doctrine is to be learnt by the neophyte or appraised by the experienced psychotherapist (of whatever school) it is essential for him to refer to originals without the labour of pursuing the German text.

The first essay gives us a general conspectus of the sexual perversions. The second shows how psycho-analysis led to the discovery that sexuality did not start at puberty, and that any previous manifestations were not necessarily pathological. On the contrary, it revealed a real infantile sexual life in every child, which was repressed and forgotten about the age of 5 and remained latent, except for occasional outbursts, till the onset of puberty. This infantile sexuality is polymorpho-perverse, and its manifestations correspond to the temporary dominance of the various erotogenous zones—oral, anal, urethral, and phallic. The third essay shows how adult perversions and many neuroses, especially hysteria, could be explained by repressions, deviations, and irregular development of these various phases. A useful summary by the author recapitulates his discoveries and the conclusions which he draws from them.

R. G. GORDON.

The fourth edition of *Manual of Clinical Laboratory Methods*, by Opal E. Hepler (pp. 387; illustrated; £2 5s.; Oxford: Blackwell Scientific Publications, 1949), intended primarily for laboratory technicians and medical students, is much larger than its forerunners. About half the book is allotted to investigations in chemical pathology, and the techniques used in haematology, bacteriology, and serology are described in fairly extensive detail. There are also short articles on pregnancy tests, tissue sectioning, allergy extracts, basal metabolism, and even electrocardiography. For most investigations one method only is described, though two or more are given for important determinations. The methods chosen are usually those popular in Britain, but a notable omission is an account of the use of the spectroscope for the detection of porphyrin, urobilin, etc. Neither is the useful property of fluorescence in ultra-violet light described. The unusual features of the book are its format and arrangement. The large size of its pages has allowed the diagrams and nomograms to be drawn on a large scale and comprehensive tables to be made. Many of the tests are arranged under a series of headings; though the use of a uniform order of description is good, one cannot avoid feeling that the author has got into difficulties in allotting numbers and letters to the various sections and headings. Nor has sufficient attention been given to the spacing between different sections, and it is not easy to find where one subject ends and another begins. There are some useful nomograms for determining the red cell indices, and there are eight good colour plates showing the maturation of blood cells and development of malaria parasites, though these were prepared too early to allow the inclusion of the tissue forms of the latter. British readers may find a few of the words and phrases used in the text unfamiliar, and they may be a little surprised by such words as "urinalysis" and "dark-field examination," and by the instruction to fill a 500-ml. "graduate" with, say, alcohol. The distinguishing characteristics of the book are its explicit technical instructions and the attention it draws to sources of error. Its introduction into laboratories may well improve the standard of work carried out in them: if references were given it would have even wider appeal.

Schafer's Essentials of Histology (15th ed.; edited by H. M. Carleton, B.Sc., and E. H. Leach, B.Sc.; pp. 655; 25s.; London: Longmans, Green) is so well known by students of medicine and biology that little need be said about it. The general arrangement and character of the work show little alteration, but there are many minor changes throughout. It is unfortunate that the account of the circulation in the kidney does not include a more direct reference to the supply of blood to the medulla, which may be physiologically important as a shunt mechanism. As a foundation for the study of physiology and of pathology the book is probably unsurpassed, and its reasonable price is a further attraction.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

A Report on the Results of Treatment of Malignant Disease in Aberdeen Royal Infirmary During the Decade 1930-1939. By J. F. Philip, M.B., Ch.M.Aberd., F.R.C.S.Ed. (Pp. 238. 15s.) Aberdeen: University Press. 1949.

The Tuberculous Process: A Conception and a Therapy. By A. Leitch, M.B., Ch.B.Ed. (Pp. 175. 12s. 6d.) Bristol: John Wright. 1949.

The 1949 Year Book of Pediatrics. Edited by H. G. Poncher, M.D., and others. (Pp. 560. $4.50 or 34s.) Chicago: The Year Book Publishers. London: Lewis. 1949.

Divine Physician. By F. L. Wyman. (Pp. 90. 3s. 6d.) London: The Bannisdale Press. 1949.

A Handbook for Industrial Nurses. By M. M. West, S.R.N., S.C.M. 2nd ed. (Pp. 264. 9s.) London: Edward Arnold. 1949.

The Africa of Albert Schweitzer. By C. R. Joy and Melvin Arnold. Concluding essay by A. Schweitzer. (Pp. 159. 15s.) London: Adam and Charles Black.

St. Thomas's Reports. Second Series. Edited by H. K. Goadby, J. S. Richardson, and others. Vol. 5. (Pp. 136. No price.) London: St. Thomas's Hospital. 1949.

Science News. 14. Edited by J. L. Crammer. (Pp. 158. 1s. 6d.) Harmondsworth, Middlesex: Penguin Books. 1949.

Handbook of Bacteriology. By J. W. Bigger, M.D., F.R.C.P., 6th ed. (Pp. 547. 20s.) London: Baillière, Tindall and Cox. 1949.

In My Mind's Eye. By F. Marion. Foreword by R. H. Thouless, M.A., Ph.D., and B. P. Wiesner, D.Sc., Ph.D. (Pp. 272. 18s.) London: Rider. 1949.

Treatment in Proctology. By R. Turell, B.S., M.D. Chapter on Psychosomatic Problems by L. Linn, M.D. (Pp. 248. 54s.) London: Baillière, Tindall and Cox. 1949.

Further Rare Diseases and Debatable Subjects. Edited by F. Parkes Weber, F.R.C.P. (Pp. 236. 25s.) London and New York: Staples Press. 1949.

Nutritional Data. Compiled by H. A. Wooster, Jun., and F. C. Blanck. (Pp. 114. No price.) Pittsburg, Pa.: Heinz. 1949.

Statistical Investigations of the Relationship of Tuberculosis Morbidity and Mortality to Infection. By S. N. Meyer. (Pp. 222. No price.) Copenhagen: Einar Munksgaard. 1949.

On Treatment of Tuberculous Cavities by Extrapleural Pneumothorax and Thoracoplasty. By M. Seip. (Pp. 131. No price.) Copenhagen: Einar Munksgaard. 1949.

Pyramideneiterungen deren Verhütung und Behandlung. By O. Voss. (Pp. 256. M. 36.) Stuttgart: Georg Thieme. 1949.

Lehrbuch der Verdauungskrankheiten. By N. Henning and W. Baumann. (Pp. 799. M. 68.) Stuttgart: Georg Thieme. 1949.

Akute Infektionskrankheiten und Hochdruck. By O. H. Arnold. (Pp. 130. M. 9.60.) Stuttgart: Georg Thieme. 1949.

Prinzipien des Lebendigen. By O. Eichler. (Pp. 99. M. 8.40.) Stuttgart: Georg Thieme. 1949.

Einführung in die Innere Medizin. By H. J. Wolf. 4th ed. (Pp. 653. M. 27). Stuttgart: Georg Thieme. 1949.

Therapeutische Technik. Edited by K. Hansen. 2nd ed. (Pp. 1,080. M. 79.50.) Stuttgart: Georg Thieme. 1949.

Endo-cavitary Aspiration. By Abdel-Raouf Hassan. (Pp. 43. No price.) Cairo: Association of Authorship, Translation and Publication Press. 1949.

La OMS y la Soberania Sanitaria de las Americas. By C. E. Paz Soldan. (Pp. 262. No price.) Lima: Instituto de Medicina Social de la Universidad de San Marcos de Lima. 1949.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY DECEMBER 31 1949

PAS AND STREPTOMYCIN

We publish on page 1521 an important statement from the Tuberculosis Research Unit of the Medical Research Council. It is to the effect that in the treatment of pulmonary tuberculosis of a certain type the administration of para-aminosalicylic acid (PAS) in addition to streptomycin has unmistakably reduced the frequency with which the patient's tubercle bacillus acquires resistance to streptomycin. Acquired resistance is the bugbear of all streptomycin treatment, and, as was pointed out recently in these columns (November 12, p. 1098), it may have peculiarly disastrous results in this disease. Recent reports[1] from the U.S.A. provide interesting information about factors affecting the development of drug resistance. There is a clear relationship with the type of lesion, frank caseation or cavity formation favouring the emergence of resistant organisms. The system of dosage also affects it, the main point being that intermittent treatment, such as the administration of a single 1-g. dose at intervals of three days or more, tends to prevent or at least delay the development of resistance. The effect of the size and number of doses during continuous treatment is more complex, but it seems that large doses, such as 3 g. daily, tend to produce highly resistant bacilli and smaller doses bacilli of intermediate degrees of resistance, most of which nevertheless are probably unaffected by further treatment. Shortening the course from 120 to 42 days had been expected to obviate drug resistance but has apparently not done so.

The advent of PAS has greatly altered the whole aspect of this problem. This substance was first shown by Lehmann[2 3] to have a pronounced action on tubercle bacilli *in vitro*, and both animal experiments and later clinical trial confirmed that this action is also exerted in the body. Feldman, Karlson, and Hinshaw[4] reported over two years ago that the drug is well tolerated by guinea-pigs and has a pronounced suppressive effect on experimental tuberculosis in these animals. Youmans and his colleagues[5] confirmed this finding in mice, though they note that PAS is inferior to streptomycin. There have been several accounts of preliminary clinical trials in human tuberculosis by Lehmann himself and others, and various forms of the disease have been treated with, on the whole, encouraging results.

There seems to be little doubt that the most valuable use for PAS will be to reinforce the therapeutic action of streptomycin. That the two drugs together exert a greater effect than either alone, apart from the advantage that the sensitivity of the bacillus to streptomycin tends to be preserved, seems evident from the recent experiments of Karlson and Feldman.[6] In guinea-pigs treated in four different ways the smallest traces of disease—represented by an infection index of 2.8—were found in animals given 4% of PAS in the diet and 2 mg. of streptomycin daily. A dose of 2 mg. of streptomycin alone gave an index of 18.2, and 6 mg. one of 3.6: thus a larger dose of streptomycin was slightly inferior in effect to the combined treatment. The index in the case of the animals given PAS alone was 27.0 and in that of the untreated controls 85.5. Clinical trial of the two drugs given together has not proceeded far enough for it to be asserted that its direct therapeutic effect is superior to that of streptomycin alone, but American workers are convinced of its value in preventing the emergence of drug resistance. Combined therapy of several kinds has been under trial in the nation-wide studies controlled by the Veterans' Administration in the U.S.A., and the conclusion reached is as definite as that in the Medical Research Council statement published to-day. Among other combined treatments, streptomycin with "promizole" did not reduce the incidence of drug resistance. Streptomycin and PAS, on the other hand, gave rise in one series of treated cases to only three resistant cultures from 26 patients (12%), whereas in patients given only streptomycin the proportion of resistant organisms isolated at the same stage of treatment was about 50%.[1]

These and similar observations have led the authorities controlling the American Veterans' Administration research programme to take an important decision: of the various methods of treatment tested in cases selected at random from patients considered suitable for treatment, all those employing streptomycin alone in whatever doses or for whatever period have been abandoned.[7] The three regimens henceforth to be tested are all 120-day courses, in each of which 12 g. of PAS is given daily together with either 1 g. of streptomycin daily, 1 g. of dihydrostreptomycin daily, or 1 g. of streptomycin twice weekly. It is clear from this decision, more than from any published data on the effects of such treatment, that American opinion is convinced of the value and necessity of using PAS in conjunction with streptomycin.

[1] Minutes of the Seventh Streptomycin Conference, Denver, April, 1949. Veterans' Administration, Washington.
[2] *Lancet*, 1946, **1**, 15.
[3] *Nord. Med.*, 1947, **33**, 140.
[4] *Proc. Mayo Clin.*, 1947, **22**, 473.
[5] *J. Bact.*, 1947, **54**, 409.
[6] *Proc. Mayo Clin.*, 1949, **24**, 510.
[7] Report of Eighth Streptomycin Conference, Atlanta, November, 1949. Veterans' Administration, Washington.
[8] *Proc. Mayo Clin.*, 1949, **24**, 213.
[9] Ibid., 1949, **24**, 220.
[10] Ibid., 1949, **24**, 544.

PAS is given by the mouth with or after meals, the dosage adopted in the U.S.A. being four daily doses of 3 g. each. It is believed to be free from any dangerous toxic effects—unless the leucopenia sometimes observed proves other than temporary—but in a large proportion of patients it causes nausea, vomiting, and diarrhoea. This has been the main difficulty in its administration: Pfuetze and Pyle[8] found that only half their patients could tolerate a daily dose of 10 g. Enteric-coated capsules do not obviate this difficulty, but the addition of sodium bicarbonate and a flavouring agent has been found helpful. The difficulty may eventually be overcome by devising a method of parenteral administration. PAS given subcutaneously in the form of its sodium salt, according to Feldman and Karlson,[9] exerts full therapeutic effect on tuberculosis in guinea-pigs, but the injections cause very severe local reactions. Possibly the final solution may prove to be the use of the chemical compound of PAS and streptomycin described by Hobby.[1] This is a freely soluble substance to which tubercle bacilli are in general more sensitive *in vitro* than to a corresponding amount of streptomycin itself. Strains resistant to it could not be produced *in vitro*. It is more effective than streptomycin in the treatment of tuberculosis in mice, and repeated injections at the same site are said to be non-irritating. More information about this substance will be awaited with much interest. A further fact to be borne in mind is that tubercle bacilli can acquire resistance to PAS itself, at least if this is given alone. Karlson and his colleagues[10] tested cultures isolated from the same patient before and after treatment; the sensitivity of the bacilli to PAS rose from 0.024 to 3.2 mg. per 100 ml. As would be expected, the resistant variant produced disease in guinea-pigs which did not respond to treatment.

THE VIRUS THEORY OF CANCER

There is general agreement that the inciting cause of cancer may be any of a number of agents, such as *x* rays or chemical carcinogens. But having started the cancer off they cease to operate, and it is then necessary to find the continuing cause. About the nature of this continuing cause there is much disagreement. Two main theories have been put forward to account for the unrestrained growth of the cells forming a neoplasm. According to the virus theory there was in the cell long before any neoplastic change occurred a virus which was living quietly in symbiosis with its host until the balance was disturbed by the inciting cause. According to the other theory the inciting cause provokes a somatic cell mutation: this is pure speculation, but appeals intuitively to some. The virus hypothesis can be experimentally proved in a small number of instances, notably in the case of the Rous fowl sarcoma, but from the great majority of tumours no virus can be separated by filtration. Those who support the theory maintain that this failure to isolate a virus from most tumours is due to technical difficulties, for it can be shown with other virus suspensions that if only a few virus particles are present they are adsorbed in the pores of the filter and do not appear in the filtrate. Professor W. E. Gye, who was director of the Imperial Cancer Research Fund laboratories at Mill Hill from 1936 until his retirement earlier this year, is a firm believer in the virus theory, and he has been active for most of his professional life in collecting evidence to support this belief. About two years ago Dr. James Craigie, well known for his studies on bacteria and viruses, joined him at the Fund laboratories, and together they initiated a new series of experiments. Some account of this work, in which their colleagues Miss Ida Mann and Dr. A. M. Begg collaborated, has already been published,[1 2] and comment on it has appeared in this *Journal*.[3] In Gye's opinion these new experiments offer definite proof of the virus theory. However, this opinion has been challenged by Dr. C. H. Andrewes in his Imperial Cancer Research Fund lecture delivered at the Royal College of Surgeons on November 29 and shortly to be published in this *Journal*. Andrewes spoke as a believer in the virus theory of cancer and described in some detail the grounds for his belief, at the same time stating why, despite the new evidence which Gye and his colleagues have brought forward, he still cannot exchange the arduous exercise of faith for the serenity of complete certainty.

The experiments described by Gye seem to show that typical non-filterable mouse tumours can in fact be transmitted by agents other than intact cells. Since it has many times been demonstrated that the presence of a virus in these tumours cannot be revealed by filtration other methods of virus detection were tried. It was found that the tumours could be minced and frozen at −79° C. for long periods and yet, after thawing and injection into suitable animals, they provoked new tumours. It is argued that no living cell could have survived this treatment; moreover, mouse-embryo tissue which will provoke embryomas on injection was rendered quite inert by such freezing. Unfortunately there is no information about the relative potency of the two preparations in causing new growths before freezing, and without this it is possible to argue that a few cells survived in both instances, but that for the production of embryomas more cells were needed than for the initiation of a new tumour: freezing had reduced the number of viable cells below the minimum necessary for the one but not below the minimum for the other. Another series of experiments has shown that tumour tissue may

[1] *Brit. J. Cancer*, 1949, **3**, 259.
[2] *British Medical Journal*, 1949, **1**, 511.
[3] Ibid., 1949, **1**, 531.

be dried from the frozen state and yet initiate tumours on re-hydration and injection into suitable animals. It is very unlikely that living cells can survive such treatment, but it is not absolutely certain that every single living cell was destroyed. In both instances it is lack of quantitative information that hinders assessment of the significance of the results.

Dr. James Craigie, who has succeeded Professor Gye as director of the Imperial Cancer Research Fund laboratories, is cautious in his remarks about the new evidence which he and his colleagues have brought forward. In the Imperial Cancer Research Fund Lecture given at the Royal College of Surgeons on November 22, and published in the opening pages of this issue, he asserts that no real progress can be made in solving the problem of whether the continuous cause of transplantable tumours is a coexistent virus until "an adequate foundation of quantitative data has been laid down." The evidence for or against will, he thinks, inevitably emerge if work is conducted towards this end. Craigie has therefore begun a series of studies which may well revolutionize cancer research. To the casual reader the preliminary work may seem mundane, for it is concerned with designs for tissue mincers, the fluids which are best for suspending the minced tissue, the way in which minced tissue may be stored and dried, and the methods of comparing the activity of different tumour preparations. But all these are points of fundamental importance if cancer research is to be put on a quantitative basis. What Craigie is now doing is to bring the more refined methods of studying viruses into the field of cancer research. Immediately ahead there lies enough work for a generation.

THE SHORT OESOPHAGUS AND HIATUS HERNIA

The condition often described as the short oesophagus is a form of hernia which may simulate a variety of clinical syndromes. The essential lesion is incompetence of the diaphragmatic oesophageal hiatus with herniation of the cardiac portion of the stomach above the diaphragm. This may sometimes pass upwards as a pouch of stomach alongside the oesophagus; in other cases the upper part of the stomach forms the hernia, leaving the thoracic oesophagus either with a normal length and tortuous appearance or apparently shortened. It is doubtful if it is correct to consider the three subdivisions as separate entities: the para-oesophageal hernia may become the oesophago-gastric, and this in turn may develop a shortened oesophagus. All three varieties are best considered under the general term of diaphragmatic oesophageal hiatus hernia. The final two words are short and alliterative, and by common usage connote the site of the herniation. The objection to describing one variety as the short oesophagus is that it implies an aetiological significance which is probably not justified. Congenital shortening of the oesophagus undoubtedly can occur, and probably accounts for the rare cases of oesophageal ulceration and stricture in children.

The majority of cases of hiatus hernia, with or without apparent shortening of the oesophagus, occur in middle-aged and elderly patients, in whom the primary defect is a weakness of an abdominal orifice. Such a weakness develops more commonly in the sthenic individual and is aggravated by the same factors which may lead to herniation elsewhere from the abdomen. It is likely that secondary shortening of the oesophagus may result from spasm of the longitudinal coat of the oesophagus: this might occur from direct irritation of the oesophagus by regurgitation of acid gastric contents causing peptic oesophagitis. If this should lead to peptic ulcer of the oesophagus shortening may then develop from cicatricial contracture, as is seen with "purse-stringing" of the lesser curve from gastric ulceration. It must, however, be mentioned that Gilbert, Dey, and Rall[1] have thought that shortening of the oesophagus could be due to a vago-vagal reflex from an intra-abdominal lesion such as cholelithiasis or duodenal ulcer, either of which are not uncommonly found with a hiatus hernia. Experiments on dogs have shown that vagal stimulation may cause oesophageal shortening, and the same result could be obtained by stimulation of the peritoneum or distension of the gall-bladder.

Dysphagia with hiatus hernia signifies severe oesophagitis or peptic ulceration. Only five patients were without this symptom in the series of 31 cases admitted to the Western Infirmary, Glasgow, during the past ten years and reported in last week's *Journal* (p. 1443) by Drs. J. B. Rennie, F. T. Land, and S. D. S. Park. Dysphagia is a relatively uncommon symptom with hiatus hernia, many of which may cause few or even no symptoms. Radloff and King[2] found dysphagia in 22% of their cases of hiatus hernia. The Glasgow series probably does not represent the total number of patients with this condition seen at the Western Infirmary, but essentially those with dysphagia as a presenting symptom. The diagnosis of hiatus hernia requires special radiological technique, and it is the responsibility of the clinician to remind the radiologist of its likelihood, for routine barium meals in a busy department may fail to demonstrate the herniation. The symptoms are protean and include unexplained haematemesis, obscure cases of anaemia, dyspepsia of all degrees—from heartburn to intense boring retrosternal pain after meals—pain simulating angina but occurring at rest or after meals, breathlessness, and cough. These symptoms may result from

[1] *J. Amer. med. Ass.*, 1946, **132**, 132.
[2] *Gastroenterology*, 1947, **9**, 249.
[3] *Proc. R. Soc. Med.*, 1949, **42**, 672.
[4] *British Surgical Practice*, 1949, **6**, 334. Butterworth and Co., London.

associated peptic oesophagitis or from the mechanical effects of the hernia. The finding of a hiatus hernia in an elderly patient may occasionally be misleading and direct attention away from a more important intra-abdominal condition. Factors causing a rise in intra-abdominal pressure may lead to incompetence at the cardia. Rennie and his colleagues draw attention to pregnancy as a possible precipitating cause of peptic oesophagitis or stricture. Lewis's[3] case of oesophagitis caused by an indwelling gastric tube suggests that another mechanism might account for the three post-operative cases included in the Glasgow series. Post-operative regurgitation of gastric contents, possibly seeping round a gastric tube in a supine, comatose patient, might cause an acute peptic oesophagitis.

Although patients with hiatus hernia and shortened oesophagus may be able to lead reasonably comfortable lives if they select their food with care and chew it well, nevertheless surgery can offer relief in many cases. The experience of Allison[4] with transthoracic repair of the hiatus hernia is particularly encouraging; in cases with much shortening and stenosis of the lower oesophagus local resection and anastomosis to the jejunum has been successfully performed.

PREGNANCY IN DIABETICS

Many workers have shown that the pattern of production of chorionic gonadotrophin (C.G.) in normal pregnancies, as reflected by its level in the blood or its excretion in the urine, is remarkably uniform. After conception the hormone rapidly increases in amount, so that between the fortieth and eightieth days of pregnancy a peak excretion occurs of 25,000–30,000 i.u. in 24 hours. There follows a rapid fall, and from the hundredth day of gestation until parturition about 4,000–10,000 i.u. are excreted each 24 hours. Departures from the norm have been claimed to occur with statistically significant frequency in pregnancies complicated by diabetes and by late toxaemia. For these observations credit is principally due to Priscilla White and to O.W. and G. van S. Smith, who have elaborated a complex theory of hormonal imbalance in a long series of papers. The characteristics of this imbalance are said to be deficiencies in production of oestrogen and progesterone by the placenta, with a reciprocal rise in C.G. levels, the latter being explained as a failure of "utilization" of this hormone by the placenta. White[1] found such an imbalance in more than 75% of patients in a consecutive series of 300 pregnant diabetics. By treatment with oestrogen and progesterone she obtained a foetal survival rate of 90%, compared with only 47% for an untreated control group (which, it should be noted, was one-third less in size), and the incidence of pre-eclampsia was reduced from 50% to 5%. The effectiveness of the treatment was ascribed to its having restored the hormone balance to normal. The Smiths[2] have maintained that late pregnancy toxaemia, which occurs frequently in diabetics, is always preceded by the hormonal imbalance mentioned above, and they have obtained encouraging results by the prophylactic administration of stilboestrol to patients whose previous pregnancies had been complicated by toxaemias. On the other hand, by no means all workers have been able to confirm these findings, either in so far as they relate to the hormone levels in blood and urine or to the effects of treatment with oestrogens. Indeed, Snaith[3] has recently reported an unexpectedly high incidence of toxaemia in a group of patients with habitual abortion treated with oestrogens, even though the proportion of live births in the treated patients was higher than would have been expected on a chance basis.

Elsewhere in this issue Dr. J. A. Loraine reports the results of his studies on the excretion of chorionic gonadotrophin by pregnant diabetic women. This careful work clears up at least some of the obscurities in the endocrinology of obstetrics, for it leaves no doubt of the existence of increased C.G. excretion in some cases of diabetic pregnancy, though the absence of a departure from normal in no less than eight out of fourteen cases is noteworthy. That the administration of stilboestrol depresses the level of C.G. excretion in both normal and diabetic pregnancies also appears to have been established beyond doubt. However, the important additional information provided by these studies is that in spite of continued administration of stilboestrol, even in increasing dosage, the C.G. excretion soon rises to, and may indeed surpass, its previous levels. Temporary interruption of stilboestrol treatment seems to restore the sensitivity of the response, at least for a time. It might, therefore, be a wise plan to administer stilboestrol in interrupted courses to these patients, if it can be accepted that depression of the elevated C.G. excretion is an object to be desired. Dr. Loraine's paper provides no evidence on this last point, since most of his patients were delivered before term by caesarean section. In no case was the baby characteristically oversize, and in one case at least mild pre-eclampsia developed while the patient was actually receiving stilboestrol. Clearer understanding of the underlying causes of these abnormalities will eventually lead to improved methods for reducing the foetal mortality and preventing the onset of late toxaemia in diabetic pregnancies.

ANIMAL EXPERIMENTS

It is constantly being asserted by anti-vivisectionist societies that animal experiments have not made any contribution to medical progress. Little attempt is made to counter this distortion of fact, for the publications and lectures of the Research Defence Society, excellent though they are, do not reach the general public. Another organization doing useful work is the Universities Federation for Animal Welfare: its handbook, *The Care and Management of Laboratory Animals*, was reviewed in the *Journal* some months ago (July 20, p. 20), and an annotation on laboratory animals appeared in the same issue (p. 26). The Federation's latest publication[1] is entitled *How to Befriend Laboratory Animals*. The sincerity of the author is obvious, and the problem is looked at from many sides by one

[1] *Penn. med. J.*, 1947, **50**, 705.
[2] *J. clin. Endocrinol.*, 1941, **1**, 461.
[3] Report of the Sixth Annual Conference on Infertility in the *British Medical Journal*, 1949, **2**, 809.

[1] Hume, C. W., *How to Befriend Laboratory Animals*, 1949. Price 3d.

deeply sensitive to the infliction of unnecessary pain on either man or beast. Not everyone will agree that "there is no reason except prejudice for preferring that an animal rather than a random human being should suffer pain," but nevertheless the general conclusions about the value of animal experiments are stated in unequivocal language. "Anyone who says that medicine, in as far as it has become scientific, does not depend on physiology, pathology, or pharmacology, or that these sciences could have progressed so far as they have without experiments on animals, is so obviously talking through his hat that he puts himself out of court and wrecks his chance of being taken seriously."

While justifying the need for animal experiments, the author of this pamphlet makes valuable criticisms. The improvement of the status of the animal attendant is important. Too often the position of "animal boy" is a despised one, and yet the care of animals requires very special abilities, and the success of experimental work largely depends on the handling of the animals before and after their time in the laboratory. Need for increased expenditure on animal accommodation is also stressed and should be considered in future schemes of development. This is particularly important in view of the need for developing techniques for the study of function by long-term experiments uncomplicated by anaesthesia. Inclusion of a veterinary surgeon among the Home Office inspectors is also an excellent suggestion. The author also does good service in pointing out the irrational attitude towards certain favoured species, notably dogs. It would seem that if the dog were exempt from experiment the causation of pain to less popular animals, such as rats, would be a matter of much less concern. No good reason exists for making such a distinction. The scientist, who does not wish to cause unnecessary pain to either dog or rat, prefers to choose his species for its suitability to his problem and not on emotional grounds. Choice of experimental animal is referred to elsewhere in this issue by Professor Samson Wright, who draws attention in a book review to the great difficulty of obtaining dogs and cats in sufficient numbers. This is undoubtedly having a deleterious effect on both teaching and research in physiology and, ultimately, on medical progress.

The present position is ridiculous. Parliament has recognized the value of animal experiments in medical research, and through licences issued by the Home Office gives protection to those doing the work. The University Grants Committee and the Medical Research Council, financed by the taxpayer and responsible to the Government, make money available for the purchase of animals which are both very scarce and very expensive. At the same time the police, under Home Office guidance and also financed by the taxpayer, assist in the collection and destruction of tens of thousands of stray animals every year, with the express aim that these shall not become available for medical research. This is both hypocritical and wasteful. Professor Samson Wright suggests an official approach by the Physiological Society to the Home Office, but it would seem that the approach might have more chance of success if supported by other bodies with wider interests. Any Government must hesitate about introducing legislation which might lose votes. But it is possible that the risk is exaggerated. A few years ago diphtheria immunization was a similar controversial subject, and now, thanks to courageous action and a well-conducted campaign of public enlightenment, it has proved to be a great boon to the health of the public.

MEDICAL PRACTICES ADVISORY BUREAU

A year ago the B.M.A. set up the Medical Practices Advisory Bureau to help doctors enter medical practice. Most of its work has been done in the field of general practice, since hospital appointments are advertised in the Press and applicants compete for them as before. But it has nevertheless been able to advise many doctors in finding suitable posts outside general practice. The most popular way of entering general practice is still by means of assistantship, and the Bureau has performed a valuable service in bringing together principals and assistants.

An unexpected finding of the Bureau's first year of work is that entry into general practice is easier than many believe, though lack of suitable housing is an obstacle in some places where an assistant or partner is sought. In general there is no difficulty in entering practice for a young man with ordinary qualifications who does not mind where he practises and is willing to accept the remuneration attached to the bottom rung of the ladder. Increasing age is a hindrance as in other walks of life, and doctors over 40 are certainly handicapped by their years. It is also regrettably true that refugees from foreign countries, among whom there are many doctors, have greater difficulty in finding openings than their British colleagues—a situation confined neither to the medical profession nor to Britain. But perhaps the greatest problem that the Bureau has had to contend with arises from the "territorial demands" of the applicants, who naturally enough often specify certain areas of the country where they wish to practise. In most cases these areas already have sufficient doctors. Even so, the Bureau has had some disappointing experiences. On several occasions it has informed over 100 doctors of a vacancy that seemed to conform with their desires, yet only a dozen or so have applied. Recently, for instance, a principal in the Home Counties earning over £5,000 a year offered a one-third share of the practice after a preliminary assistantship of twelve months, the share rising to two-fifths in five years, and to 48% in ten years. A small modern house was available to rent at 30s. a week. The Bureau sent the details to more than 130 doctors: fewer than 20 responded.

Now that general practitioners are gaining experience of the Health Service many of them who a year ago were doubtful about taking assistants or partners are deciding to do so. At present the Bureau is filling about 50% of the vacancies referred to it, whereas nine months ago the figure was about 30%. Certainly the Bureau has found no evidence to support allegations that principals tend no longer to seek partners but prefer a succession of assistants. As the director said in his report[1]: "Contrary to expectation, there seems to be an increasing tendency for the retiring doctor to wish to preserve the practice as an entity by securing the introduction of a 'logical

[1] *British Medical Journal Supplement*, 1949, **2**, 226.

successor' or by taking in a partner for a longer or shorter period."

The services of the Bureau are free to members of the B.M.A., and that doctors are finding it useful is clear from the steady increase in the numbers who seek its help. Its offices are at B.M.A. House in London, at 7, Drumsheugh Gardens, Edinburgh, and at 33, Cross Street, Manchester.

VITAMIN C AND BENZENE POISONING

Having observed that the symptoms of scurvy resembled those of benzene poisoning, Meyer[1] carried out the experiment of giving large amounts of ascorbic acid to guinea-pigs in order to find out if they became more resistant to benzene: he found that they did. Friemann[2] measured the output of ascorbic acid in the urine of men exposed to benzene fumes and found it reduced, and Forssman and Frykholm[3] observed signs of vitamin-C deficiency in the majority of 26 men exposed to benzene fumes, as compared with 23 men in the same industry who were not exposed to the fumes. The relation between vitamin-C deficiency and exposure to benzene fumes has now been more fully studied by Ekman,[4] who used large numbers of guinea-pigs and came to the following conclusions. Guinea-pigs exposed to benzene vapour daily lose weight and die. The administration of large amounts of ascorbic acid gives some protection, since they gain weight and not all of them die: to obtain complete protection the guinea-pigs must be given not only ascorbic acid but also cucumber or citrin. Cucumber contains large amounts of ascorbic acid oxidase, an enzyme which increases the breakdown of ascorbic acid in the body. Ekman considers that this oxidase accelerates the rate at which ascorbic acid breaks down the benzene molecule. Thus the protection given against benzene by ascorbic acid and cucumber depends on the fact that these agents furnish a means of destroying cyclic compounds like benzene.

PAIN OF VISCERAL ORIGIN

The mechanism of visceral pain is still a matter for speculation, mainly because it is difficult to obtain reliable factual information. The investigator is dependent on the patient's interpretation of the sensations which various manœuvres may provoke. Furthermore, the patient may be under the influence of drugs at the time or affected by a very natural anxiety. Nevertheless, certain constant responses have been noted, and recent investigations have added fresh information about visceral sensitivity. The earlier teaching that the viscera are at all times insensitive to ordinary stimuli must be modified in the light of the findings of Kinsella,[5] Brown,[6] and Bentley.[7] There can be no doubt that an inflamed or diseased area in a viscus can be tender to direct pressure, and even normal organs —for instance, the testes—may be sensitive. The pain is not well localized, due partly to the relatively small numbers of afferent nerves from the viscera and partly to the sensorium being uneducated to interpret these rare sensations. As a result, the tendency is to relate the pain to the embryonic position of the viscus. Bentley[8] has demonstrated that the afferent fibres travel via the splanchnic nerves, since he found that splanchnic block abolishes the tenderness of a peptic ulcer. Stretching or spasm of the muscle of the hollow organs of the abdomen causes pain which is mediated by the same nerves. Such pains may be associated with voluntary guarding, but not as a rule with true involuntary rigidity. This latter is largely dependent, as Morley showed, on irritation of the parietal peritoneum and, with acute local tenderness, is the most reliable sign of inflammation in the abdomen.

Though it seems clear that visceral and parietal irritation causes distinct sensations of pain carried by different nerves, the question remains whether there is a place for Mackenzie's old theories of the viscero-cutaneous reference of pain and of viscero-motor reflexes. So far as the abdomen is concerned there is little need to invoke these hypotheses, except perhaps for the unilateral rigidity of renal colic. But the radiation of pain in angina pectoris is difficult to explain otherwise, and the concept of an irritable focus in the spinal cord has recently been reintroduced to account for certain ill-understood painful states in the upper limbs.[9] Though much remains to be learned, it is now possible to interpret with fair accuracy pain and tenderness due to visceral disease.

MEDICINE, 1900–50

Anyone born in the year 1900 probably likes to think of himself as a child of the twentieth century. But according to the Astronomer Royal he is not; he belongs apparently to the nineteenth century. The cause of the disappointment is that there was no A.D. 0, or at least no A.D. 0 has been admitted by the chronologists. The error having started so far back, no one has yet had the common sense to say outright that the first century by some mishap contained only 99 years. If this convenient and charming fiction had been adopted there would not have occurred at intervals of 50 years since pedantic discussions about the beginning and end of centuries. According to *The Times*[10] Kaiser Wilhelm II declared firmly that 1899 was the last year of the nineteenth century. To-day we find ourselves in the much better company of France, whose Ministry of Justice has decreed that on Sunday, January 1, 1950, France will enter the second half of the twentieth century.[11] On the reasonable assumption that 50,000,000 logical Frenchmen cannot be wrong, this *Journal* in its issue of January 7 will celebrate the first half of the twentieth century by publishing a special symposium on the theme "Fifty Years of Medicine." It will do that firm in the conviction that at least no one will hesitate to celebrate January 1, A.D. 2000, as a remarkable date in the history of the human race.

Dr. Howard Nicholson will deliver the Goulstonian Lectures before the Royal College of Physicians of London (Pall Mall East, S.W.) on Tuesday and Thursday, January 10 and 12, at 5 p.m. His subject is "Suppurative Pneumonia."

1 *Z. Vitaminforsch.*, 1937, **6**, 83.
2 *Arch. Gewerbepath. Gewerbehyg.*, 1936, **7**, 278.
3 *Acta med. scand.*, 1942, **128**, 256.
4 *Acta Pharmacol. Toxicol.*, 1947, **3**, 261.
5 *Brit. J. Surg.*, 1940, **27**, 449.
6 *Lancet*, 1949, **1**, 994.
7 *Ann. R. Coll. Surg. Eng.*, 1948, **3**, 328.
8 *Ann. Surg.*, 1948, **128**, 881.
9 Steinbrocker, O., Spitzer, N., and Friedman, H. H., *Ann. intern. Med.*, 1948, **29**, 22.
10 December 17, 1949.
11 December, 18, 1949.

TREATMENT OF PULMONARY TUBERCULOSIS WITH PARA-AMINOSALICYLIC ACID AND STREPTOMYCIN

PRELIMINARY REPORT

A clinical trial of *p*-aminosalicylic acid (PAS) and streptomycin in pulmonary tuberculosis was undertaken in 1948 by the Medical Research Council, with the co-operation of the British Tuberculosis Association. The trial is not yet completed, but certain results already obtained are of such importance that the joint committee responsible for guiding the trial has decided to issue the following preliminary statement.

A major disadvantage in the use of streptomycin is that the period of effective therapy is limited in many patients by the emergence of streptomycin-resistant strains of tubercle bacilli after five or more weeks of treatment. It has been thought by many workers that the addition of another tuberculostatic agent might be sufficient to suppress the resistant strains, which in the initial phases are present in very small numbers; published reports on a few cases treated with PAS and streptomycin have been encouraging. The present investigation was planned to examine, by the method of controlled trial, the possibility that PAS has this property, and at the same time to assess the clinical effect of this drug alone and in combination with streptomycin Accordingly, three treatment groups of over 50 cases each were observed: (*a*) PAS alone (20 g. of the sodium salt daily); (*b*) streptomycin alone (1 g. daily); and (*c*) both drugs together (20 g. of the sodium salt of PAS and 1 g. of streptomycin daily). The methods were similar to those employed in the first M.R.C. clinical trial of streptomycin in pulmonary tuberculosis (*British Medical Journal*, 1948, **2**, 769), and the type of case was again defined as follows: acute rapidly progressive bilateral pulmonary tuberculosis, of recent development, unsuitable for collapse therapy, in young adults aged 15 to 30. After acceptance for the trial by a panel, patients were allocated to one of the three treatment groups by a method of random selection. The prescribed treatment was given for three months in each case. Clinicians and pathologists at eleven hospital centres have co-operated in this investigation, keeping uniform records, employing standard clinical and bacteriological procedures, and reporting results at regular intervals to the Council's Tuberculosis Research Unit, where the grouped results have been analysed.

For this well-defined type of case of pulmonary tuberculosis the trial has demonstrated unequivocally that the combination of PAS with streptomycin reduces considerably the risk of development of streptomycin-resistant strains of tubercle bacilli during the six months following the start of treatment. This conclusion is applicable so far only to the acute form of disease treated, and it remains to be seen whether the same results are obtainable in other forms of tuberculosis amenable to streptomycin therapy. Furthermore, the conclusion is applicable only to the large dose of PAS used; this dosage causes discomfort in some patients, and it has been agreed to find out, by further trials, whether smaller doses would achieve the same result. It must be stressed also that streptomycin is effective only in certain forms of tuberculosis, and the finding reported here must not be interpreted as indicating that a combination with another drug will be effective in those forms in which little result would be expected from streptomycin alone.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

ANALGESIA IN CHILDBIRTH

BY

C. LANGTON HEWER, M.B., M.R.C.P., F.F.A. R.C.S.

Senior Anaesthetist, St. Bartholomew's Hospital

One of the first facts the medical student is taught when starting his course in obstetrics is that labour is a physiological function. It does not take him long to find out that however physiological the process may be it is usually accompanied by pain, which may be severe. To alleviate this pain without danger to mother or child has been a problem facing obstetricians and anaesthetists for over a century: now it is known that not only the mother but the baby benefits from painless childbirth.

Suggestion

It can safely be said that there is no known method of achieving general or local analgesia with drugs which may not either affect the course of labour or have some deleterious action on the mother or foetus. The only absolutely safe method of analgesia is that obtained by suggestion, one form of which is associated in this country with the name of Dr. Grantly Dick Read. The theoretical basis of this technique depends upon the assumption that fear causes a sympatheticotonia which makes the circular fibres of the cervical sphincter contract. In turn the longitudinal fibres of the upper uterine segment increase their tension to overcome the obstacle, and eventually the threshold of pain is crossed—"A tense woman means a tense cervix and a long and painful labour." This is probably an over-simplification of a complicated process, but there is no doubt that antenatal suggestion combined with relaxation at crucial times of the labour can work wonders with a co-operative patient. Unfortunately, this technique makes heavy demands on the doctor's time and patience, and in these days it is frequently impracticable.

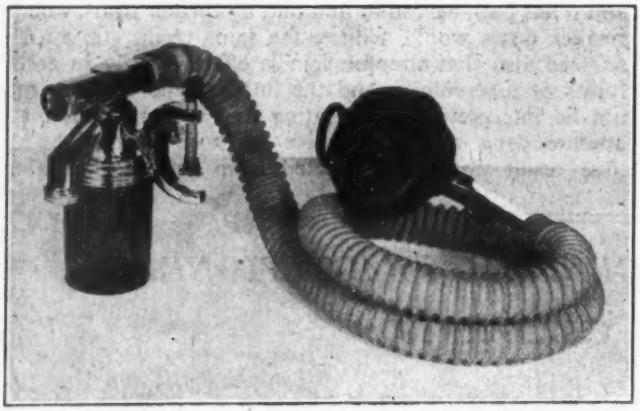
General Analgesia by Volatile Drugs: Chloroform

All volatile anaesthetics are to some extent analgesic when given in subnarcotic concentration, and most of them have been employed in this way in obstetrics. Chloroform analgesia has been in use for over a century, and the method is known as "à la reine," since John Snow practised it on Queen Victoria in 1853 during the birth of Prince Leopold. Chloroform analgesia is still widely used in rural areas of Great Britain, and general practitioners often fit up some type of Junker's apparatus and mask so that the patient

can obtain relief by hand-pumping. If chloroform must be used, Mennell's bottle is probably the safest auto-inhaler as it cannot be upset and is difficult to overfill. The tubes cannot be connected up wrongly, and the vapour concentration is normally insufficient to produce loss of consciousness. Capsules containing 20 min. (1.2 ml.) of chloroform have also been used: they could be crushed and placed under a mask to produce analgesia. Although it is probable that primary cardiac failure is less likely to occur during labour than at other times, chloroform is a toxic drug to both mother and child and its use is not to be encouraged.

Trichlorethylene

"Trilene" (purified trichlorethylene) has largely replaced chloroform as an analgesic in labour, since there is no doubt that it is less toxic to the liver and much less likely to cause primary cardiac failure. The most popular auto-inhaler in this country is Freedman's, a "draw-over" apparatus which delivers a vapour concentration of about 0.65% trilene in air. A hole near the facepiece must be covered by the patient's finger before trilene vapour can be inhaled, and thus acts as a safety device. This method is so convenient and reliable that an investigation was instituted by a committee of the Royal College of Obstetricians and Gynaecologists to see whether it could be used by unsupervised midwives. A study of 2,354 cases showed that the technique was most efficient, only 7% of the mothers being



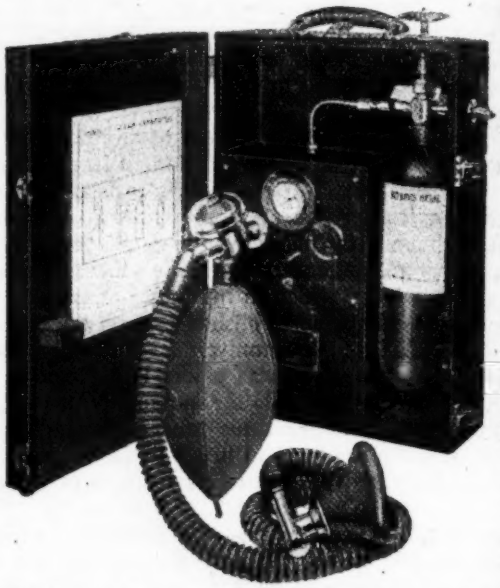
The Freedman inhaler. (By permission of A. Charles King, Ltd.)

dissatisfied with the relief obtained. There was no evidence of increased risk to mother and child, but the committee did not recommend that legislation be passed for the method to be used without medical supervision. Other "draw-over" inhalers have been devised with which the vapour concentration can be varied to suit the individual patient, one of the simplest and most efficient being the "cyprane." The Oxford ether vaporizer can also be used for the same purpose; 7.5% on the ether calibration is equivalent to approximately 1.5% trilene.

Nitrous Oxide and Air

Nitrous oxide and air analgesia was popularized in 1933 by Minnitt, who adapted a McKesson oxygen-therapy apparatus for the purpose. Modern machines deliver about 45% nitrous oxide in air and work on the intermittent-flow principle, so that no gas escapes when the patient raises the facepiece. The air-hole normally covered by the patient's finger acts as a safety device. Gas and air should not be started too early in labour, and certainly not before the uterine contractions are causing discomfort. This will probably be at about five-shillings dilatation of the cervix. It is essential that inhalation be started at the very first warning of a pain. Between the pains, restful sleep is usually obtainable.

During the second stage of labour, inhalation of gas and air is stopped at the height of a pain and the patient asked to bear down while holding her breath. Further inhalations of the mixture can be taken after each effort. As the head



The Minnitt gas-air apparatus (portable model). The Chassar Moir attachment has been added to the delivery tube where it leaves the machine. With the cylinder valve open the 2.5-litre bag will fill with pure nitrous oxide—the first three or four breaths will be of nitrous oxide alone, after which the patient inhales the standard nitrous-oxide–air mixture. (By permission of A. Charles King, Ltd.)

is crowned, continuous inhalation should be given until the birth of the child, the patient being instructed not to bear down.

Pure nitrous-oxide–air analgesia administered from an approved apparatus is the only form of inhalation which may be given without medical supervision by midwives trained in its use. Since July, 1946, all pupil-midwives must take a course of instruction and be found proficient before enrolment as midwives. Nitrous-oxide–air analgesia is extremely safe and non-toxic apart from the slight risk of anoxia. The analgesia is, however, not always so complete as is desirable and the onset is rather slow. The former disadvantage can be overcome by adding a trace of trilene vapour to the mixture by some device such as a Rowbotham's bottle plugged into the circuit. A more rapid onset of analgesia can be obtained by starting each inhalation with two to three breaths of pure nitrous oxide followed by the gas-air mixture. A Chassar Moir attachment enables this to be done. It must, however, be clearly understood that any modifications to standard machines disqualify midwives from using them without supervision. The weight and bulk of the necessary apparatus constitute a definite disadvantage when gas-and-air analgesia is used in domiciliary practice. In addition to Minnitt's apparatus certain other types of intermittent-flow machines, such as the "Amwell" and the "Jecta," are recognized as safe for use by midwives.

Nitrous Oxide and Oxygen

The substitution of oxygen for air diminishes the risk of anoxia but renders the method impracticable for midwives and increases the bulk and weight of the apparatus. It is,

however, probably the safest form of inhalation analgesia for obstetrics and tends to shorten the course of labour by increasing the force of the uterine contractions. During the birth of the child a brief period of anaesthesia is easily obtained, but some obstetricians hold the view that from a psychological aspect it is better for the mother to retain consciousness. Light narcosis is desirable, however, should perineal sutures have to be inserted.

Analgesia by Non-volatile Drugs

In 1902 Von Steinbüchel and Gauss introduced "twilight sleep," which consisted of an initial injection of morphine and scopolamine followed by supplementary doses of scopolamine alone. Some analgesia and considerable amnesia resulted, but the frequent prolongation of labour resulting in the birth of a narcotized baby soon diminished its popularity. Most obstetricians now feel that morphine and its derivatives should seldom be used before the birth of the child.

The many non-volatile drugs which have been tried as substitutes for morphine include rectal paraldehyde and bromethol ("avertin"), and oral barbiturates such as pentobarbital ("nembutal"). More recently pethidine and physeptone have been employed, but unfortunately all these drugs tend to diminish uterine contractions and to depress the infant's respiration. It is impossible in this article to give details of the various techniques, or even to mention the many combinations of drugs which have been tried.

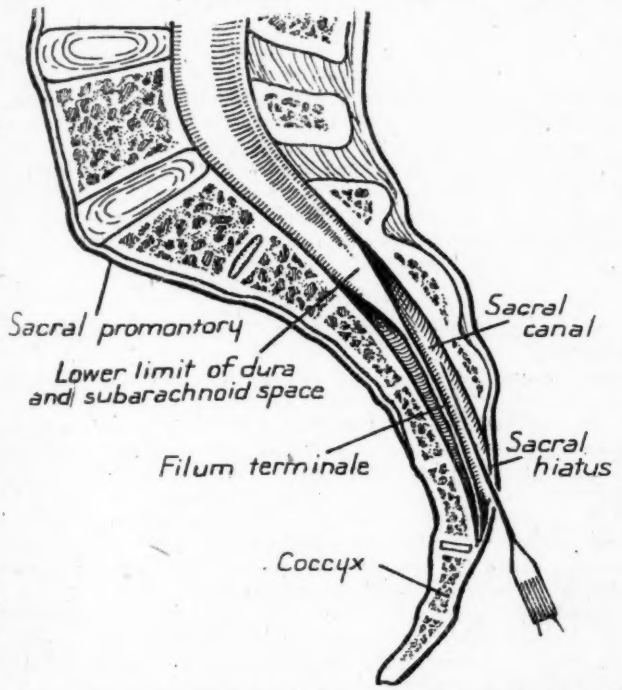


Diagram to illustrate the principle of caudal analgesia. The analgesic solution is injected through the sacral hiatus to render the nerves in the sacral canal insensitive, but remains outside the dural sac.

Intravenous procaine has also been used, and is said to be satisfactory. It is injected as a slow intravenous drip in a dilution of 1% in 5% aqueous glucose solution. It should be noted that it is unwise to exceed the rate of injection of 20 mg. of procaine per minute, or tachycardia, muscular twitching, and finally convulsions may ensue.

Local Analgesia

In order to be successful local analgesia for childbirth must obviate the pain both of the uterine contractions and of the dilatation of the birth canal. The method known as fractional caudal block has come to the front recently, and extremely good results are claimed for it. Very briefly, the technique consists in the insertion of a malleable needle or a ureteric catheter through the sacral hiatus into the caudal canal and injecting at intervals an analgesic solution such as 1% procaine. It should be clearly realized that this technique alters the whole course of labour. The patient has no urge to bear down or to use her abdominal muscles in the second stage, so that this is usually prolonged, while interference with the normal flexion of the head and rotation of the occiput result in an unusually high proportion of occipito-posterior presentations. The incidence of forceps deliveries is also increased. The insertion of the needle may prove difficult or impossible, particularly in fat patients, and inadvertent spinal block is a possible complication. Furthermore, sepsis and broken needles are not unknown. It will therefore be seen that the method demands a skilled team working in hospital, and it is outside the scope of the general practitioner. In an emergency some relief can be obtained from the pain of stretched tissues by infiltration on each side of the midline half-way between the anus and the edge of the perineum.

Spinal analgesia has been given a good trial, and, though it still has some advocates, the general feeling is that it is unsatisfactory for labour. There would seem to be an overaction of the circular fibres of the uterus combined with underaction of the longitudinal muscle, so that the organ contracts violently with diminished expulsive power. This would appear to be borne out by the fact that spinal block is frequently successful in the treatment of post-partum haemorrhage due to uterine atony.

Conclusions

From the foregoing remarks it will be obvious that there is an almost infinite choice in the possible techniques of analgesia for childbirth. There are bound to be considerable differences of opinion about their relative merits, but my own views are as follows:

(1) If an experienced anaesthetist is available, the safest and best method is nitrous-oxide–oxygen inhalation, intermittent during the pains of the late first and second stages and continuous during the birth of the child.

(2) If a general practitioner is present, the midwife can give trilene and air under his supervision with some type of auto-inhaler such as Freedman's. Alternatively, the gas, gas-air sequence can be used with the Chassar Moir attachment to a Minnitt's apparatus.

(3) If only the midwife is present, inhalation of a gas-air mixture from an approved machine is the only permissible method.

(4) If the delivery is taking place in the service of an obstetrical unit at a large hospital some local technique such as fractional caudal block may prove excellent.

It should be mentioned that only normal labours in healthy mothers have been considered in this article. Pathological conditions may necessitate some modifications of the analgesic technique.

The Scientific Film Association is conducting for its information service a national survey of makers, owners, and users of scientific films. It would be glad to be informed of the name and address of the makers of such films, the gauge and running time, and a brief synopsis of contents. Particulars of the association's work may be obtained from the secretary at 4, Great Russell Street, London, W.C.1 (Telephone: MUSeum 2403).

BRITISH ORTHOPAEDIC ASSOCIATION

ANNUAL MEETING

The annual meeting of the British Orthopaedic Association was held at Bristol from October 13 to 15 under the presidency of Mr. S. A. S. Malkin (Nottingham).

Orthopaedic Surgery and Traumatic Surgery

A discussion on the relationship of orthopaedic surgery to traumatic surgery was opened by Mr. William Gissane (Birmingham). He said that 80% of patients were admitted to casualty departments because of accidents, and only 10% required reference to the medical or general surgical departments. The casualty department had often proved a barrier to prompt and effective treatment, and control of these departments might justly be claimed an orthopaedic commitment. Fractures provided but a small part of the work of accident services. Accident hospitals like that at Birmingham could be developed for a population of about two million people, and should receive at once, both on economic and on clinical grounds, injuries of a specialized nature. An accident unit should retain and develop its relationship with surgery as a whole, and every accident hospital should be attached to a teaching hospital. After preliminary experience in general surgery and full training in orthopaedic surgery, intending traumatic specialists should acquire at least the first principles of plastic surgery and thereafter gain practical knowledge of the work of a special accident unit.

Mr. E. A. Nicoll (Mansfield) said that traumatology was now practised in three ways: in conjunction with orthopaedics; as part of general surgery; and as a specialty in its own right, a status which was hardly yet justified, and which in any event was inseparable from an orthopaedic training. Better distribution of orthopaedic surgeons was required.

Mr. H. Osmond-Clarke (London) considered that accident units should usually be situated in general hospitals, maintaining close contact with teaching hospitals. Whether the surgeon confined himself to traumatic work or not, training in general and orthopaedic surgery was essential. Mr. Rainsford Mowlem (London) emphasized the importance of full co-operation in any traumatic unit between plastic and orthopaedic surgeons. Mr. R. H. Metcalfe (London) referred to one Metropolitan region in which registrars had been enabled to gain a varied experience by working in rotation through appointments in casualty departments, wards, consultative out-patient departments, and long-stay orthopaedic hospitals.

Mr. Bryan McFarland (Liverpool) considered that an accident unit should be within a general hospital, with an orthopaedic surgeon in charge. The co-operation of a plastic surgeon in the treatment of injuries and in the training of orthopaedic specialists was desirable. Miss M. Forrester-Brown (Bath) referred to the Ontario scheme of postal advice upon radiographs. The president hoped that this expedient would not be followed. Mr. H. Langston (Southampton) considered that Mr. Metcalfe's scheme for registrars was excellent, pending the formation of large accident units.

Mr. Norman Roberts (Liverpool) said that the accident unit should be situated in a general hospital. The casualty department should be controlled by the accident service and directed by the orthopaedic surgeon. Mr. J. C. Scott (Oxford) deplored the inadequate orthopaedic training of many traumatic surgeons. Mr. E. N. Wardle (Liverpool) regretted the frequent appointment of the most junior member of a general hospital staff to the casualty or accident department. Mr. Roland Barnes (Glasgow) advocated an accident unit under the control of the orthopaedic department in every teaching hospital.

Professor George Perkins (London) thought it was generally agreed that everyone practising orthopaedic or traumatic surgery must be properly trained, and also that traumatology was not to be encouraged as a specialty. The president took the same view and said that practical experience was more important than a special degree. The emphasis should be on training in general orthopaedic surgery, and thereafter on special training in the principles of plastic surgery and traumatology.

Lesions of the Lumbar Intervertebral Disk

Mr. J. Pennybacker (Oxford), on the basis of 800 cases, mentioned first the importance of differentiation from cases of neoplasm, which were often misleading in their symptoms, but in which the neurological signs were usually progressive. Occasionally radiographs would show scalloping of the vertebral bodies or increased width between the pedicles; lumbar puncture usually revealed an increased protein content of the cerebrospinal fluid, and as a rule myelography established the diagnosis. Other conditions which might cause difficulty in diagnosis were tuberculous arthritis, metastatic carcinoma, and spondylolisthesis.

No lesion was found at operation in 3% of cases. Naffziger's sign and pain on lumbar pressure with the patient prone were important diagnostic aids. Treatment should follow the lines of rest in bed, a plaster jacket for six weeks, and thereafter a corset, operation being reserved for cases which were resistant or in which there were frequent recurrences. Manipulation was dangerous. Exploration must be extensive, including the fourth and fifth lumbar and the first sacral roots without laminectomy; both sides should be explored and the theca opened. Arthrodesis was usually performed only if relief was incomplete.

Mr. E. N. Wardle (Liverpool) regarded retropulsion of a disk as secondary to loss of equilibrium of the whole spine and loss of elastic reaction in many disks. A plaster jacket, applied in head suspension, had given complete relief in 60% of cases. Mr. J. R. Armstrong (London) detailed the causes of operative failure. Sometimes there was no lesion, or, more often, exposure was at the wrong level or a midline disk lesion made disclosure difficult. A double lesion was found in about 20% of cases; a bilateral lesion might need exposure on both sides. In some cases insufficient removal might allow further protrusion; or a previously healthy disk might prolapse. In other cases a nerve root might be damaged or might become adherent; there might be arthritis of intervertebral joints. Arthrodesis at the time of the first operation he condemned as unnecessary. It increased the complications and danger, and demanded a more prolonged post-operative immobilization. Where it was necessary, arthrodesis could more conveniently be undertaken later; it was difficult to repeat an operation on a nerve root after an unsuccessful arthrodesis.

Other Subjects

A number of short papers were presented on a variety of subjects.

Protrusions of Cervical Disks.—Mr. G. L. Alexander (Bristol) referred first to nerve root compression. He ascribed the frequent involvement of the sixth and seventh cervical roots to their thickness; the eighth cervical root, also thick, escaped because its course was less oblique and it was less prone to stretching by cervical and shoulder movements. In cord compression the symptoms and signs were often confused; lumbar puncture seldom helped, but myelography might. Cord compression called for laminectomy and removal of the displaced material. Operative results were imperfect.

Lambotte.—Professor J. Verbrugge (Antwerp) painted a vivid picture of Monsieur Lambotte, an early pioneer of bone suture. At 85 this versatile and ingenious surgeon still operated occasionally.

Fractures of the Upper End of the Radius in Children.—Mr. C. C. Jeffrey (Birmingham) confined his remarks to fractures through the neck of the radius and separation of the upper epiphysis. Most were abduction injuries, the position of the forearm determining the direction of the tilt, which could be estimated before reduction by radiography in various positions of rotation. Closed reduction was performed by digital pressure on the radial head in an appropriate degree of rotation with adduction of the elbow. The late results were good provided the radial head had not been completely displaced. Occasional premature fusion was much more likely if there had been complete separation, and would lead to deformity of the head of the radius and limitation of movement.

Experimental Rupture of the Medial Ligament of the Knee.—Mr. E. A. Jack (Edinburgh) had studied the results of

experimental rupture of the medial ligament of the knee in the cat. Ligamentous recoil always left a gap which could no longer be closed after seven to ten days. Healing occurred except when the rupture was at the upper end of the ligament. These experiments suggested that the ligament should be sutured during the first week, with the least possible damage to its blood supply.

Experiences in Mauritius.—Mr. J. M. Fitton (Mauritius) described the island's peculiarities and the orthopaedic service which had been developed since 1945, when an epidemic of poliomyelitis occurred. Mr. H. J. Seddon (London) referred to the magnitude of Mr. Fitton's task and his modesty. Other Colonial orthopaedic centres had now been established in Malta, Nairobi, and Lagos. It was imperative that the men who built up these centres should find places on their return home.

STAFF COLLEGE FOR HOSPITAL ADMINISTRATORS

KING EDWARD'S HOSPITAL FUND FOR LONDON

At a meeting of King Edward's Hospital Fund for London held on December 14 at St. James's Palace, H.R.H. the Duke of Gloucester said that the management committee had been giving careful consideration to the ways in which the Fund's resources could best be used. They now sought approval for three main proposals.

It was proposed that a sum of £100,000 should be placed again at the disposal of the Distribution Committee for grants to hospitals. The second proposal involved the allocation of £80,000 to the Convalescent Homes Committee. Thirdly, there were grouped together a number of activities and projects.

Some of these are already well known, for example, the Emergency Bed Service. Others, such as the division of hospital facilities, the staff college for ward sisters, the training school for medical records officers at the Middlesex Hospital, and the projected training centre for hospital caterers at St. Pancras Hospital, were discussed at previous meetings, and have been described in the *Journal*.

The most important new proposal is the establishment of a residential staff college for hospital administrators. On this subject there have been consultations with the Institute of Hospital Administrators, and the Fund has already acquired suitable premises. Mr. Constable, the present house governor of St. George's Hospital, has agreed to resign his hospital appointment and he will become the first head of the new college. Some months must elapse before the college can be opened, but it is already assured of the support of the Ministry of Health.

At the same meeting Sir Wilson Jameson pointed out that in the metropolitan regions there were more than 120 hospital management committees each with a chief administrative officer, and there were, in addition, several hundred senior officers in charge of unit hospitals. Though hospital management called for special inborn qualities of mind and spirit, he thought that much could be done to develop and strengthen these qualities by an enlightened system of training. In some countries training in hospital administration was provided by universities, but in England such provision on any scale was most unlikely, though in the teaching of the subject some of the methods of university instruction might well be used. A college of the kind now proposed—in part residential for students, in part a centre for the exchange of ideas between existing administrators, members of boards and management committees, doctors, nurses, and others connected with hospital work—would do much to raise the standard of hospital administration in this country.

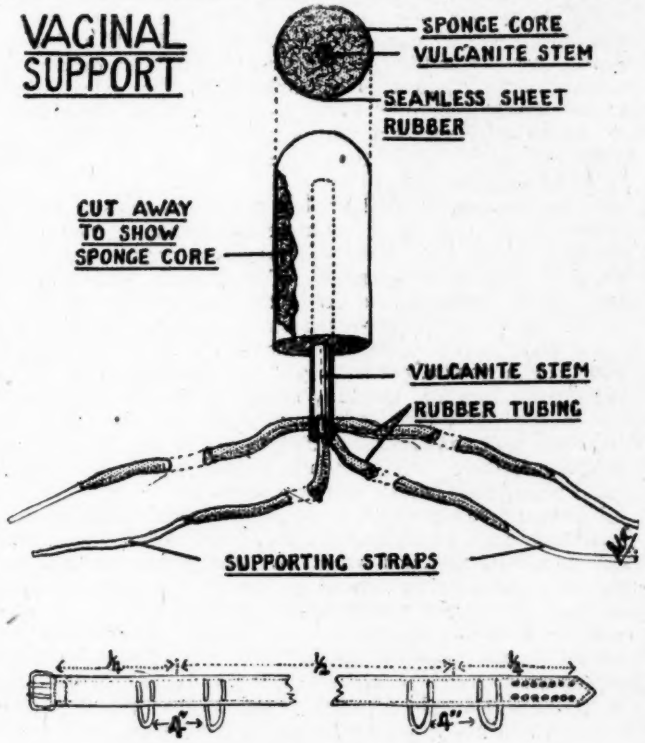
Yugoslavia has made a voluntary contribution of $10,000 to the Supplementary Budget of the World Health Organization for 1950. WHO's regular budget is $7,500,000, but an additional $10,000,000 has been requested from member States in voluntary contributions for the development of health programmes.

Preparations and Appliances

A NEW TYPE OF VAGINAL SUPPORT

Dr. DAVID L. ARNOLD, D.R.C.O.G., writes: In the hope that some measure of relief may be afforded to those who are condemned to a life of semi-invalidism on account of a uterine prolapse for which surgical relief cannot be given, I bring the following appliance to the notice of practitioners.

The first case in which the support was used was one of a thrice-recurrent vaginal vault prolapse. The patient was a married woman aged 62, and was unable to move about without extreme discomfort and pain. She refused to undergo a Le Fort operation, but wished to have some sort of relief from her symptoms. A Napier cup-and-stem pessary was tried, but one week later she still complained of discomfort, and it



was found that the rim of the pessary had ulcerated the vagina over a large area; it was therefore decided to try to design a more comfortable support.

The pessary here illustrated was made and fitted to the patient. It was arranged that its diameter should comfortably fill the vagina, leaving the urinary meatus free of the body of the support, and ½ in. (1.25 cm.) below its base. It is made of rubber sponge with a sheet-rubber covering and a vulcanite stem, and is supported by a waistband and four straps as used in the cup-and-stem pessary. The patient wears the pessary during the day, inserting it with a little "dettol" cream each morning, and removing it after retiring at night. It is washed and placed in a weak solution of dettol during the night and is ready for use next morning. She has been using the support for two years and continues to be entirely satisfied with it.

Five other cases of procidentia unfit for operation state that the appliance is a success.

It is not suggested that the support should be used in an operable case of prolapse, but it may be of value in any post-menopausal case in which operation is contraindicated. Its advantage over the cup-and-stem pessary is that the pressure area is evenly distributed over the vagina and not confined to one small part.

The appliance is made to order by Messrs. Allen and Hanburys, Ltd.

Reports of Societies

SOME ASPECTS OF UNDERNUTRITION

A meeting of the Section of Experimental Medicine of the Royal Society of Medicine was held on December 13, under the presidency of Professor G. W. PICKERING, when the subject of undernutrition was discussed.

Miss E. M. WIDDOWSON described an experience in 1946 in the British Zone, in the industrial town of Wuppertal, Westphalia. At that time the official German rations provided 1,050 calories a day for the normal consumer. Very few of the population, however, lived as normal consumers. There were many supplementary rations, for one or other of which almost everybody was qualified. The most extraordinary supplement was 30 eggs for the donation of half a litre of blood. Anyone certified as suffering from hunger oedema or as more than 20% underweight also qualified for extra rations in addition to any other extra allowance they might have. Moreover, these supplementary allowances were not the only means of getting extra food; everyone who had a garden cultivated it most diligently.

All the patients certified by their doctors as cases of hunger oedema had to go to a clinic before obtaining their extra rations; it was from these clinics that a group was drawn for more detailed investigation. These people were suffering from calorie deficiency, but not of the most severe type. They looked pale, and it was obvious from their clothes that they had lost a good deal of weight. Oedema was more common in men than in women, particularly in men over 40; it was confined to the legs and generally disappeared after a few days' rest in bed. No signs of vitamin deficiency were seen and there were no complaints of diarrhoea. So far as could be ascertained, there were no deaths in the British Zone which could be attributed solely to undernutrition.

Nineteen men were selected for an unlimited feeding experiment, their ages ranging from 26 to 80 years, and they were given unlimited food for eight weeks. All of them at the beginning showed signs and symptoms of undernutrition; all but two had oedema, and all but one were underweight. They had all been short of food for the previous 18 months. Their first "unlimited" meal was breakfast, at which one of them, aged 80, consumed in margarine, cheese, sugar, and bread the equivalent of 3,170 calories. The men had an unlimited supply of potatoes and other vegetables, tinned meats, dried milk, and cocoa. After a few weeks some were eating less than at first, but others were eating increasing amounts. The average calorie intake during the period was about 6,000 a day, compared with a previous 1,800 or 1,900. These 6,000 calories were obtained from 200 g. of fat, 200 g. of protein, and rather more than 800 g. of carbohydrate. The increase in the amount of food caused no digestive disturbance. The average gain in weight was just over 10 kg. The two octogenarians gained 10.3 and 9.5 kg., respectively. There was no significant change in blood pressure as a result of the feeding. The serum protein rose from 6.4 to 7.1 g. per 100 ml., entirely due to the rise in the globulin fraction.

At the end of the eight weeks, although a few of the men had lost some of their oedema, in others it was worse, and the frequency of the distribution of the various grades of oedema was the same as at the beginning of the experiment. A marked feature was the polyuria, especially at night. The men finally returned to their former rations, which, even when supplemented, amounted to only about one-third of the calories they had been receiving. It was possible to follow the progress of these men during the next two years. At first their weight fell sharply, but with better feeding for the community generally their condition improved considerably.

Professor R. A. MCCANCE spoke briefly on serum cholinesterase. The level of serum cholinesterase, he thought, was a measure of the general metabolic condition or plane of nutrition. For assessing the general nutritional level of a group of 50 or 60 people estimation of the serum cholinesterase level was about as good as any other single test, perhaps better than most. It agreed closely with estimates of the nutritional state from clinical and other tests. But it was good only for group testing. There was considerable variation individually even among normal people, so that it was not much use estimating the serum cholinesterase level of a single person and relating it to the normal average. The other interesting thing about serum cholinesterase was that everything known about it suggested that it had species specificity. Variations with the plane of nutrition, so far as could be discovered, applied only to man.

Birth-weight and Lactation

Dr. R. F. A. DEAN discussed the effect of undernutrition on the size of the baby at birth and on lactation. At Wuppertal the British investigators were fortunate in finding a maternity hospital which had escaped damage during the war, and at which the most meticulous records had been kept for 15 years.

In 1946 a pregnant woman in the British Zone was entitled to food providing about 2,400 calories a day. When she was feeding her baby later she was entitled to 3,500 calories. About 1,200 women in the clinic were interviewed; about half of them said that they got less than 2,400 calories, and 20% said that they got a little over the ration. Nearly all the women wanted more fat. One pint of milk a day was allowed during pregnancy and three pints during lactation. The women were not obviously undernourished and none of them had oedema. They might have been, on a rough estimate, 8% underweight at the beginning of pregnancy. Abnormalities of pregnancy during 1946–7 were not greatly different from those of 1937–8. The average birth-weight in 1937–9 had been about 3,340 g.; in 1945 the average was 3,155. There was a big drop in this respect in the first quarter of 1945, and a further drop in the second quarter, but towards the end of that year there was some recovery. The average daily milk yield of the mother at about the fifth to the ninth day in 1937 was about 320 g.; in 1945 it was 240 g.

It seemed, then, that during the time of the acute food shortage in Germany the children were smaller at birth, and that the mothers had more difficulty in establishing lactation. It was difficult to account adequately for these findings. Some diets which were analysed provided 2,500 calories and contained about 25 g. of animal protein in 75 g. of total protein. It might be that the diet of the women did not contain enough animal protein or that in one way or another it did not provide a good mixture of amino-acids. The psychological upset to which these women had been subjected had, of course, to be considered.

It was possible to follow the growth of 300 children born in 1946 during about six months in 1947–8. The children who were small at birth were nearly always brought up to the average, sometimes quite rapidly, as a result of good feeding. It seemed unlikely that the German children, who now had what food they needed, would show any signs of the hard times during which they were born.

EPIDEMIOLOGICAL RESEARCH ON VIRUS DISEASES

At a meeting of the Devon and Exeter Medico-Chirurgical Society on December 1 Dr. F. O. MACCALLUM spoke on the part played by the general practitioner in epidemiological research on virus diseases.

Virus diseases, Dr. MacCallum said, were coming out of the laboratory and into the field. By taking accurate notes of even a few cases the general practitioner could add to the sum of knowledge in this direction, as had already been done by Dr. Pickles, of Wensleydale. Incubation periods could be verified by noting single and only possible contacts. Material for the diagnosis of virus diseases was readily obtainable by the general practitioner. Material was wanted for laboratory investigation in cases of suspected influenza. There were many

questions to be answered. Where did influenza go in the summer? Where did an influenza epidemic start? Vaccines prepared and given in advance might confer immunity to influenza, but it must be confessed that they were often ineffective owing to a change of strain in the virus.

Cases of atypical pneumonia, characterized by acute onset, intense headache, malaise, depression, hacking cough, and absence of fever or other physical signs were probably due to virus infections. One of these infections—so-called Q fever, due to *Rickettsia burneti*—appeared, at any rate in a proportion of cases, to be milk-borne. The incubation period was 14-25 days, and rashes were rare. The rickettsia could be excreted symptomlessly by cows, sheep, and goats for as long as three months, and had been found, though rarely, in cattle ticks and dog ticks.

No serological tests were yet available in this country for differentiating strains of the virus of poliomyelitis. The viruses responsible for a large group of cases labelled "encephalitis" had still to be worked out. The syndrome of lymphocytic meningitis was probably caused by many different viruses. In 80 of 100 cases investigated the virus had not been identified.

Finally Dr. MacCallum pointed out that the distribution of cowpox in this country had not yet been fully mapped, and he asked for scrapings from suspected cowpox lesions.

Correspondence

Colour Plates

SIR,—I am grateful to Professor L. J. Witts for his kind remarks (December 10, p. 1336) about my *Atlas of Bone-marrow Pathology*, but I am disappointed to find that he does not like the colour plates. This is, I am well aware, very much a matter of individual preference, and Professor Witts prefers the lithographic type of reproduction of which Blackfan, Diamond, and Leister's *Atlas of the Blood in Children* is a first-class representative.

There are, however, other views. The *Journal of Pathology and Bacteriology*'s (1948, **60**, 648) review of my book said: "In tone, colour, and perfect register these plates do real justice to the skill of the artist, Miss Davison, and are among the very best available in haematological literature. Some of the cells appear small, but they are all drawn to the same scale and their size is actually that which one is accustomed to see with the magnifications usually employed." This last phrase gives the key; the reviewer understands that what I was trying to do was to reproduce the appearances seen down the microscope by those whose job it is to examine bone marrows for diagnostic purposes.

The lithographic illustrations of the *Atlas of the Blood in Children* are beautifully done, but many of the pictures, especially of the more primitive types, show types of cells that are only occasionally seen through the microscope in a blood or marrow film; the plates could not be used for day-to-day help in the laboratory—and were probably not designed for this purpose. Many of the cells in my plates appear not wholly distinct, because that is how they looked. I insisted on a high fidelity of reproduction from the original paintings, and Messrs. Heinemann deliberately rejected the lithographic process because they considered it not good enough to give the results desired. They went to immense trouble to ensure the right "tone, colour, and perfect register." I and Messrs. Heinemann embarked on this production because the many atlases in existence did not, in fact, show actual appearances; most of them showed fine, often very fine, reproductions of paintings of idealized type cells, and the best of the pre-war atlases, that published by Schulten in Germany, was no longer available.

This dilemma, whether to prepare fine reproductions of idealized type cells or whether to endeavour to reproduce actual appearances at the sacrifice of an artificial clarity, has to be faced whenever a colour atlas is contemplated using paintings from which to work. Professor Witts prefers the former; I think the latter of more practical value. Presumably, if colour photomicrography can be sufficiently improved, photographic reproduction will solve the question for us; but that time is not yet.—I am, etc.,

Manchester. M. C. G. ISRAËLS.

Hormones and Rheumatism

SIR,—Dr. Hans Selye's account (November 19, p. 1129) of his most recent work on the adrenal cortical hormones and their inhibiting effect on the development of arthritis makes fascinating reading. I am particularly interested in his interpretation of the results of one experiment.

Fifty rats were divided into five groups, one of which served as controls. The remainder were deprived of food for 24 hours and subjected to various forms of trauma or "stress"—exposure to cold, forced exercise, spinal transection, and injections of formalin—and as a result of these procedures some of the animals were obviously debilitated but others appeared to be in good condition. After subsequent injections of formalin into the paw the controls all developed "formalin arthritis," while the "treated" groups did not. In his interpretation of these results Selye rejects the possibility that the development of lesions was repressed by debility, since some of the animals were obviously in good condition. Instead he suggests—and in your leading article (p. 1159) you agree with him—that the "stress" provoked secretion of ACTH, which in turn stimulated gluco-corticoid production, the last being responsible for the inhibition of arthritis.

For some years I have been intrigued by the effect of debility on the development of lesions in disease. In the case of leprosy[1] and chronic rheumatism[2] I have pointed out that all the agents known to be effective in the suppression of lesions shared a common factor which I referred to as debility but which Selye, perhaps more accurately, describes as stress. I had put down the recession of lesions to the depressing effect of the debility on the reaction of the tissues. While I feel I have no right to dispute Selye's interpretation of this particular experiment, the extensions of this interpretation are sufficiently important to merit discussion.

"Cortisone" release through stress will explain the good results in rheumatism which follow parathyroidectomy and mock parathyroidectomy, fracture of a long bone, hysterectomy, or any major surgical operation. It will explain the effects of gold and atophan poisoning. But what of the success of local measures? Selye's rats injected with formalin between the shoulder blades failed to develop arthritis in the paws. I had believed that such measures as acupuncture, application of Corrigan's button, osteotomy, surgical manipulation, and local injections of distilled water, lactic acid, bee venom, and so on acted locally and produced local effects. While they were generally believed to raise the resistance, I choose to believe that they lowered it by depressing tissue reaction. If these effects are indeed achieved through release of cortisone generally, why should not an injection of lactic acid, say, into the hip cure arthritis in the knee, and why should not manipulation of the elbow improve movements in the ankle? I have discussed this question of local debility following trauma in the paper on rheumatism referred to above. I am convinced that local trauma or interference can operate locally to suppress the development of lesions without the intervention of cortisone.

In discussing the effects of debilitating agents in rheumatism I referred to the reputed efficacy of toxic doses of vitamin D. Here one would now say was a "stress" reaction with cure by cortisone effect. Will cortisone cure lupus, which yields even more spectacularly to vitamin D in toxic doses? And was the previous cure of lupus by Finsen-lamp treatment due to the depressing effect of local trauma or general release of cortisone? Dermatologists, so far as I know, treated all the lesions. Again, I had believed that the cure of general paralysis by malaria could be attributed to the effect of the general debility on the development of anatomical lesions in the brain. I also thought that the local trauma occasioned by the use of convulsants or leucotomy was the agent which repressed the exaggerated behavioural reaction of schizophrenia. Now it

appears that the alarm reaction of malaria or convulsant therapy could release cortisone, which is the final curative agent. But why then are not malaria and leucotomy interchangeable as therapeutic agents?

One more consideration. The effect of stress factors in preventing the development of lesions is beautifully illustrated in the epidemiology of poliomyelitis and in experimental studies of the infection in monkeys. There is the time-honoured observation that the disease attacks only the healthiest children in the community; the incidence is heavy in country districts and light in the towns; heavy in the suburbs and light in the slums; heavy in the well-cared-for children of countries with low infantile mortality and negligible in undernourished tropical children; higher in American whites than negroes; higher in officers than in men; higher in the autumn, when food and vitamins are more plentiful, than in the spring, the season of scarcity, of pellagra and rickets. Experimentally various forms of trauma and malnutrition lower the incidence of disease or give complete protection. Local trauma to the nose and throat region by application of caustics—including, incidentally, formalin—will lower the incidence of the disease. So will deprivation of thiamine or riboflavin. The agents which Selye used to provoke an alarm reaction in rats are all obviously potent in the prevention of poliomyelitis. Selye believes, and you concur in his belief, that these agents finally release cortisone, which prevented or cured formalin arthritis. Do you, Sir, accept the obvious extension of this interpretation of Selye's results? We must wait patiently, I suppose, for increased supplies of cortisone, when practical trial may provide the answers to our questions.—I am, etc.,

Bristol. WILLIAM HUGHES.

REFERENCES

1 *Trans. R. Soc. trop. Med. Hyg.*, 1938, **31**, 383.
2 *Ann. rheum. Dis.*, 1942, **3**, 89.

Failed Forceps

SIR,—In discussing the management of occipito-posterior positions of the foetal head and deep transverse arrest your correspondent, Mr. Derek Freeth (December 3, p. 1298), states, "The correct procedure is, of course, the application of Kielland's forceps and not the displacement of the head above the pelvic brim during further attempts at rotation."

I am fearful that this will make many practitioners who have had to seek further assistance in a case of "failed forceps" feel that if only they possesed a pair of forceps with straight blades all would have been well. While not denying that the use of such an instrument may be attended with excellent results in expert hands, I would draw attention (1) to the words of Alan Brews,[1] "It is not easy to use except for an expert who has made himself well acquainted with it"; (2) to one of the few statistical reports on the use of this instrument and to the fact that it shows a higher foetal mortality than with traditional methods,[2] and (3) Monro Kerr's beautiful description of the technique of manual rotation, where stress is laid on the importance of rotation of the shoulders as well as the head.[3]

The successful management of such cases is dependent on an accurate assessment of the position of the foetal head and the skilled use of the hands and not upon whether one buys a new pair of forceps or not.—I am, etc.,

Norwich. A. P. BENTALL.

REFERENCES

1 Eden, T. W., and Holland, E., *Manual of Obstetrics*, 1948, London, p. 727.
2 *Clinical Report of Queen Charlotte's Maternity Hospital*, 1932–3.
3 *Operative Obstetrics*, 1937, London, p. 90.

SIR,—With reference to the letter by Dr. Mabel F. Potter (December 10, p. 1353) I should like to have further particulars. At what stage of labour does she proceed to "spin the occiput"? Is it after full dilatation of the os, before or after rupture of the membranes, and is anaesthesia required? It puzzles me also how pressure with "three fingers on the occiput" could produce flexion of the head. I should have thought it would have extended it further. Further elucidation of these points would be gratefully received.—I am, etc.,

Rhyl, Flints. AUSTEN H. HOLMES.

SIR,—Since two correspondents, Mr. W. P. Hirsch (November 19, p. 1179) and Mr. Bryan Williams (December 10, p. 1353), have stated that there is inadequate consideration of transverse arrest of the head in the standard textbooks in this country, I would respectfully point out that they will find three pages devoted to this particular subject, as well as numerous references in different sections, in *Operative Obstetrics* (Munro Kerr and Chassar Moir, 1949, London).

I would implement the information contained therein by saying that there is no necessity to apply Kielland's forceps in the original manner, but that the "wandering method" with the anterior blade is excellent. This manœuvre removes the danger which has for long been held against the instrument—namely, rupture of the lower uterine segment. There is still another method of putting on the anterior blade when the head is low enough, and that is by direct application. One can easily feel the anterior ear just behind the symphysis pubis in these circumstances, making diagnosis of position easy, and the anterior blade can be directed between the baby's head and the symphysis pubis without disimpaction.

A combination of low spinal analgesia and Kielland's forceps, I believe, is the best method for dealing with transverse arrest of the head, whether deep or otherwise, and for occipito-posterior positions. The operator supplies the extra force required to effect delivery and imitates Nature's mechanism at the same time. I can state, and support with statistics, that foetal mortality is thereby reduced.—I am, etc.,

Oxford. G. GORDON LENNON.

SIR,—I consider that Dr. Mabel F. Potter's letter (December 10, p. 1353) is most misleading. It would appear that confusion exists regarding the definition of persistent occipito-posteriors. I have always understood this to mean direct occipito-posterior (i.e., occipito-sacral). It is established, and I have myself observed, that in many of these cases the head is already well flexed.[1] Hence, if Dr. Potter's interpretation of persistent occipito-posterior is the same as my own, it is difficult to appreciate why flexion—using H. L. Hodge's manœuvre (*Principles and Practice of Obstetrics*, Philadelphia, 1864)—results in anterior rotation.

I can only assume that she refers to occipito-posteriors lying in the oblique position; which leads one to wonder what term she applies to occipito-sacral positions. Furthermore, we know that some 70% of oblique occipito-posteriors rotate spontaneously, so any manœuvre would seem meddlesome unless adequate time has been allowed for this to occur.—I am, etc.

London, N.W.8. R. E. FFRENCH DEVITT.

REFERENCE

1 De Lee, J. B., and Greenhill, J. P., *Principles and Practice of Obstetrics*, 1947, Philadelphia, p. 539.

Operative Treatment of Varicose Veins

SIR,—Mr. R. R. Foote (December 3, p. 1295) quotes me as stating "that elastic-adhesive bandage should not be used in the treatment of varicose ulcer." I advise against the use of an "elastoplast" type of bandage—i.e., one which owes its stickiness to a rubber-zinc spread, because many patients are sensitive to it. This rubber-zinc type of bandage is more adherent and elastic than that spread with the lead paste, and it suits a large number of patients when it is properly put on, but in my hospital clinics its ill-effects are well known and patients fear its application. For this reason I have given up its use. A test for allergy to this elastoplast type of bandage is by the application of a piece of it, the size of a shilling, to the leg: if there is no redness the next day then it can be safely used on that person. I have found that the old-fashioned emplastrum saponis type (diachylon or "lestreflex"), which is also reasonably elastic and adhesive, is almost universally acceptable and equally effective.

As regards Dr. H. M. Hanschell's remarks (p. 1296) on my results, I would say that one pulmonary embolism in a thousand is rather less than the incidence after any clean operation below the diaphragm. With regard to my two cases of deep thrombophlebitis, they affected the leg only and not the thigh.

Both were slight, so that neither heparin nor dicoumarol was used; they responded progressively to compression bandaging. I think that the danger with the method used carries no greater risk from embolism or deep thrombosis than any other clean surgical procedure of similar magnitude. For instance, I recently followed up 300 routine herniae in patients over 50 years old; there were two deaths from pulmonary embolism and one temporarily swollen leg and thigh. Further, these varicose vein results are those of my assistants and myself, the former performing rather more than half.

Dr. Hanschell says, "In an unselected run of over 1,000 patients whose varicose veins are left unabraded and uninjected neither deep thrombophlebitis nor pulmonary embolism is to be expected." I wonder if instead of "is to be expected" he meant "occurred"? None of us expect complications after our clean operations, but . . .—I am, etc.,

London, W.1. H. DODD.

*** This correspondence is now closed.—ED., *B.M.J.*

New Mechanism of Vitamin Deprivation

SIR,—In his reply to my letter (November 19, p. 1177) Professor A. C. Frazer (December 3, p. 1294) states that his original paper (October 1, p. 731) deals with vitamin deficiency in the sprue syndrome. When this statement, as it seems to do, means "in the sprue syndrome only," it is incorrect, since the paper is concerned with the general aspect of vitamin deficiencies. This is obvious from the following items.

(1) The title, "A New Mechanism of Vitamin Deprivation, with Special Reference to the Sprue Syndrome."

(2) From many parts of the text, particularly the introduction, which deals with deficiencies not only of B vitamins but also of vitamins A and D, which are entirely unconnected with the sprue syndrome.

(3) The following passages of the last paragraph of the paper: "This paper is especially concerned with vitamin deficiencies in the sprue syndrome. Special consideration must be given, however, to the possible importance of intestinal bacterial competition in other conditions. A similar competition situation must arise in pernicious anaemia, in which vitamin-B deficiencies are well recognized. . . . The possibility of intestinal bacterial competition along the lines indicated in this paper should be investigated not only in the sprue syndrome but in various other conditions which are thought to be closely associated, such as pernicious anaemia, pellagra, and nutritional megalocytic anaemia (Manson-Bahr, 1940, 1941). The metabolic demands of a varying but essentially non-pathogenic flora may be the key to the problem of the multiple but selective vitamin deficiencies so commonly observed in these conditions."

If Professor Frazer had restricted his discourse to the sprue syndrome alone, as he does in his letter, I would not have commented on it, as I did not do on his former paper[1] on a similar subject but concerned with the sprue syndrome only. I have no personal experience with the sprue problem and I never pretended to deal with it. My comments were based on experience of nicotinamide deficiency as influenced by intestinal bacteria. All of Professor Frazer's replies which rejected my comments as invalid for the sprue syndrome can therefore be dismissed. They have been directed against the claim of having discovered a new mechanism of general vitamin deprivation, which he now withdraws or denies to have had in mind. There are many points in Professor Frazer's letter that would need reply. I limit myself, however, to a few of them.

Professor Frazer is perfectly correct in saying that I do not differentiate between the effects of the administration of natural and of synthetic vitamins. I had always accepted the fundamental pharmacological rule that the action of a chemical compound does not depend on the mode of its origin. Professor Frazer is, however, wrong in saying that I do not differentiate between the effects of different routes of administering the vitamins. A whole paper[2] has been devoted to this problem. I wonder on which experimental evidence Professor Frazer's statement on release or consumption of B vitamins by intestinal *Bact. coli* is based.

I have to apologize for "misquoting" a sentence of Professor Frazer's article by omitting the word "normal" before "human subjects," but this is materially irrelevant, because the investigations quoted were carried out on physically fit persons as well as on pellagrins, and not, as Professor Frazer wrongly states, on deprived subjects or those treated with sulphonamides. From the differences in nicotinamide methochloride elimination before, during, and after administration of succinylsulphathiazole, which changed the composition of the intestinal flora, conclusions were drawn on the importance of these bacteria for the vitamin requirements of the human body.

I fully agree with the statement of the reviewer[3] quoted by Professor Frazer that the full significance of the bacterial synthesis of vitamins by human intestinal bacteria for the vitamin requirements is not yet fully known, but this knowledge can be attained step by step by careful experimental examination only.—I am, etc.,

London, S.W.1. P. ELLINGER.

REFERENCES

1 *British Medical Journal*, 1947, **2**, 641.
2 Ellinger, P., and Hardwick, S. W., ibid., 1947, **1**, 672.
3 Najjar, V. A., and Barratt, R., in *Vitamins and Hormones*, 1945, **3**, 23.

Vagotomy for Peptic Ulcer

SIR,—In the article by Messrs. I. M. Orr and H. Daintree Johnson on the above subject (December 10, p. 1316) we get the surgeons' point of view. We are now anxious to hear what the physician has to say about it. Meanwhile it would not be amiss to have the opinions of general practitioners, for after all it is they who have to guide the patient in arriving at a decision. The doctor thus asks himself, "If I have a peptic ulcer, would I submit myself to vagotomy?" I should say, "Definitely not." Why undergo the trouble and risk when one can quite well control the secretory activities of the vagus with atropine sulphate in gradually increasing doses? Some disagreeable symptoms are apt to follow vagotomy and it is rather a let-down when, after stopping the secretion of acid, the surgeon has to administer hydrochloric acid to stop the diarrhoea which ensues. He has also found that the best results follow vagotomy plus resection of the ulcer or a gastro-enterostomy.

But I have patients working regularly and apparently cured—some after gastro-enterostomy without vagotomy and others treated solely by medical means—and I maintain that uncomplicated peptic ulcer can be cured by this latter treatment if, and it is a big "if," the patient carries out his instructions faithfully not only for three months or so but for the remainder of his life. For I consider that such ulcers come under the heading of "deficiency diseases," like pernicious anaemia and diabetes. The normal, healthy stomach must form a secretion to protect the mucosa from the digestive action of its own juices. When this is deficient or absent ulceration is prone to develop. It is a permanent condition and therefore ulcers are apt to recur and may be multiple. It is significant that ulcers induced by traumatism in the stomachs of healthy animals heal rapidly.

One can quite understand why uncomplicated ulcers heal after vagotomy, which renders the stomach inert and changes it from an organ of digestion into a mere receptacle, and an uncomfortable one at that, since once the food gets in it is difficult for it to get out again owing to impaired motility. In the medical treatment of peptic ulcer I have learnt that it is imperative to give oils and cream before meals in the endeavour to supply a substitute for the natural protective secretion of the mucosa.—I am, etc.,

Upholland, Lancs. J. THOMSON SHIRLAW.

Aureomycin in the Treatment of Pneumonia

SIR,—Dr. J. G. Scadding's article on "The Management of Acute Pneumonias in Adults" (November 26, p. 1225) prompts me to write of a case I have attended recently.

A male aged 46, weighing 17½ stone (110 kg.), who indulges considerably in alcoholic beverages, came home on November 12, 1949, from watching a football match, feeling shivery and ill. He went to bed and called me in next morning. He was in a very dyspnoeic state with a continuous irritating and non-productive cough, and he complained of severe pain in his left epigastrium, radiating to

the left shoulder-blade and increasing with the slightest movement. He was obviously very ill. His temperature was 103° F. (39.5° C.). His abdomen was very distended. On percussion of the left hemithorax there was dullness of the lower two-thirds, with absence of vibration, the cough revealing crepitations in the upper limit of the dullness. Diagnosis of lobar pneumonia was made. He received 500,000 units of penicillin and 2 g. of sulphadiazine. He had the same amount of penicillin twelve-hourly and 1 g. of sulphadiazine four-hourly until November 22. During these ten days no great change was noticed in his general condition except a slight decrease of the fever. A radiograph taken on November 18, although unsatisfactory because of great technical difficulties in handling a very ill and obese patient, showed a large patch of hepatization of the lower left lung and a small amount of fluid in the costal diaphragmatic margin on the same side.

Penicillin and sulphadiazine were stopped on November 22, and he received 500 mg. of "aureomycin" at 6 p.m. on November 23 orally. This was repeated six-hourly until the total dose was 4 g. The response was dramatic: at 9 p.m. his temperature was 98.4° F. (36.8° C.) and the next day his condition was indeed changed—pain had disappeared, the cough became productive, there was no dyspnoea, and the dullness was less pronounced. His condition continued to improve, and on November 28 his lungs were clinically clear.

Unfortunately the unproductive cough made it impossible to examine the sputum at the beginning, but there was no doubt I was dealing with a case of a penicillin-and-sulphonamide-resistant pneumonia. The immediate response to aureomycin, so easy to administer and without any side-effects, will have to be considered in future in such pneumonias.—I am, etc.,

London, W.1. M. KENIG.

Pathological Fracture Treated by Methyl Testosterone

SIR,—The following case history shows how an ununited pathological fracture of the femur due to metastases from carcinoma of the breast united under the influence of methyl testosterone.

A woman aged 50 was admitted to hospital on March 12, 1948, having sustained a fracture of the middle of the shaft of the left femur after a fall in her home. Five years previously she had had a right radical mastectomy performed for carcinoma of the breast, and this was followed by a course of deep *x*-ray therapy. *X*-ray examination showed a complete transverse fracture of the middle of the shaft of the left femur with areas of rarefaction in the adjacent bone. The pelvis showed multiple areas of increased density due to metastases. *X*-ray examination of the chest showed the lung fields clear.

The fracture remained in perfect position on light traction and subsequently a plaster spica was applied. On September 30, 1948, the fracture was quite ununited clinically and the radiograph showed no callus at all. It was kept in position by strapping extension and a Thomas splint, but by this time the patient's general condition had greatly deteriorated. She was very feeble, was vomiting repeatedly, and required large doses of sedatives daily. On October 25—i.e., after the fracture had been ununited for seven and a half months, the patient being by this time in a state of advanced cachexia—methyl testosterone, 20 mg. three times daily, by mouth was commenced. This was increased to 30 mg. t.d.s. on November 4. She began to improve rapidly, vomiting ceased, and in a few weeks she was able to take full diet. No further sedatives were required and she put on weight. On December 10 her general condition had improved remarkably and she was mentally bright, but large masses were palpable in the abdomen rising from the pelvis. A hard fixed mass could be felt in the pouch of Douglas, and there was a pleural effusion on the right side. The fracture by this time felt firm clinically, and *x*-ray examination showed good callus formation—i.e., after seven weeks on methyl testosterone.

Subsequently she developed gross ascites, bilateral pleural effusions, and oedema of the legs, and she died on January 12, 1949. Necropsy by Dr. Keith Simpson showed advanced carcinomatosis in the chest and abdomen, with massive deposits in both ovaries. There were also deposits in the skull, spine, and pelvis. The left femur was dissected out and found to be soundly united by bone. There was apparently no growth in the shaft of the femur.

Pathological fractures due to metastases from carcinoma of the breast do, of course, frequently unite if properly immobilized. The recalcification of bony metastases from carcinoma of the breast under the influence of methyl testosterone is now well known. The interest of this case lies in the striking (though temporary) improvement in the clinical condition, and the rapid union following methyl testosterone administration of the pathological fracture after non-union for seven and a half months. The temporary effects of methyl testosterone and its lack of influence on the soft tissue growth are noteworthy. Adair's[1] findings are thus confirmed in this case. His observations lead him to recommend intermittent treatment with methyl testosterone, a second course being followed by further improvement.—I am, etc.,

Whipps Cross Hospital, London, E.11. S. G. NARDELL.

REFERENCE

1. *Proc. R. Soc. Med.*, 1949, **42**, 468.

The Stability of Society

SIR,—As a mere medical student it is with extreme trepidation that I engage in a joust with Lord Russell. There were, however, one or two points in his erudite, if rather ethereal, Lloyd Roberts Lecture (December 10, p. 1307) to which I would like to draw your attention.

We are told that medical missions in China "do much to diminish the infant death rate; the consequence is that more children die painfully of famine at the age of 5 or 6. The benefit to mankind is very questionable." Medical missions would indeed be gratified if they had reduced the infant death rate by even a fraction of the "much" quoted, and the subsequent aside is hardly relevant to the argument. Is there one law for the Chinese and another for the European? Do we not pride ourselves on the improving record of antenatal and postnatal care? Is such care to be applauded in England and to be condemned in China?

World-wide advocacy of birth control or suitably controlled outbreaks of plague are suggested as means to keep down the world population. Surely a cheaper and more practical method would be for doctors to liquidate their patients instead of to heal them. The chronically sick and infirm, the aged, and the mentally subnormal could be dispatched and thus reduce the number of hungry mouths to be fed. This idea is not so fanciful as it might appear, as we all remember such experiments being carried out in Germany in recent years.

Surely the fundamental error in Lord Russell's thesis is that he tends to regard men *en masse* and not as individuals. He is asking people with hopes and fears and aspirations to submerge their identity in a homogeneous mass. They must forgo the joys and privileges of parenthood because perhaps in fifty years trouble may befall their descendants. I say, God bless those who work among the sick and suffering in China or India or any other country. Let us do all we can to help our fellow men wherever they are in need.—I am, etc.,

London, E.1. JOHN TESTER.

A Sign of Ruptured Ectopic Gestation

SIR,—There are few constant clinical signs in medicine, but I would like to draw attention to one which is, I think, insufficiently recognized. I refer to the loss of consciousness which invariably accompanies the rupture of a Fallopian tube due to an ectopic pregnancy. This is by no means meant as an original observation, for it is mentioned in many places, but it does deserve more prominence, as it may easily be the deciding sign in what may be a difficult diagnosis. I would go further. When one is faced with the usual picture of some six weeks' amenorrhoea, bleeding, and abdominal pain, and if careful questioning elicits a loss of consciousness, however momentary, at the onset of the pain, the diagnosis, in 100% of cases, is a ruptured tube.

This sign does not refer to a tubal abortion, which is different in pathology, symptoms, and prognosis, but I hope I am not labouring the point too much if I again use the word invariable, for I believe this sign to be constant. As such, therefore, it is of the very greatest diagnostic value, and deserves greater prominence than it has hitherto been given.—I am, etc.,

London, W.1. MORTIMER REDDINGTON.

POINTS FROM LETTERS

The Acute Throat

Dr. H. TUDOR EDMUNDS (Slough, Bucks) writes: I am sure many practitioners will feel indebted to Dr. T. Anderson (October 15, p. 860) for his clear exposition on the "Acute Throat" in general practice, but it is surprising he does not mention under the heading of treatment the importance of elimination therapy in throat infections. . . . There is a tendency to-day to over-emphasize the importance of the individual germ and forget the patient. . . . There is an old-fashioned remedy for throat infections which is so simple it is likely to be scorned in these days of complex treatments, but which, if tried, will surprise many practitioners of the younger school. At the onset a brisk purge is given, then calomel, ¼ gr. (16 mg.) t.i.d., for three to five days. This dose can be the same for child or adult. The patient is encouraged to take large quantities of fruit juice and water as well as fruit pulp, and a blanket bath is given daily.

Weight Reduction

Dr. P. L. DESHMUKH (Poona) writes: I have been greatly interested in the correspondence on weight-reducing diet for personal reasons as well as in the interest of my patients. The letter of "Apollonian" (July 28, 1945, p. 136) and the subsequent correspondence was a great incentive to me to reduce my own weight. I found his plan very austere. I could maintain myself on it for barely a week doing full work and sport. But then I had to give it up, for the pangs of the plan were enormous for me. There was significant loss of weight for the period, but it soon relapsed to its original level very rapidly. . . . An essential principle in weight reduction, which is often lost sight of, is the stabilization, periodically, of the lower levels of weight reached. It is no use simply going on reducing, for when the restrictions slacken, as they are bound to slacken some time, the weight will start increasing with a vengeance. To prevent this a weight-reducing plan must include a "weight-stabilization" programme. This can be achieved by "re-educating" or "rehabilitating" the metabolism to a lower level or "tune." . . .

Chilblains

Dr. GORDON AMBROSE (Carshalton Beeches, Surrey) writes: Now that we are well into the chilblain season, I think it might be interesting to your readers that I have seen cases of painless swelling of the fingers, and in one case of the toes, following the use of calciferol. I hasten to add that these cases were young women: two were taking halibut-liver-oil capsules, and one was having a course of ultra-violet light at the local hospital for "rheumatism" before and during her course of calciferol. Metabolic disturbances with high doses of vitamin D are well recognized. The effect of painless swelling of the fingers in young women appears out of all proportion to its medical seriousness, and it appears worth while to stop all other sources of vitamin D during a course of calciferol.

Angioneurotic Oedema Caused by a Bee-sting

Dr. C. W. A. SEARLE (London, S.W.5) writes: Having read the letter by Surgeon Commander W. R. S. Panckridge and Surgeon Lieutenant C. Q. Henriques (December 10, p. 1354) I am inclined to report a very similar case which occurred in Ahmednagar, India, in March, 1941. I was called to see the wife of the brigade major, who was said to be in great distress, having just been stung by a bee. I saw her within half an hour of having been stung and her condition was exactly similar to that described by the two authors referred to. I also gave a subcutaneous injection of 0.5 ml. of liquor adrenalin, with dramatic effect. Within a few minutes oedema of the glottis had subsided, followed by that of the lids, which was very marked. Within half an hour a clinical cure was effected. She then gave me a history of having been stung by a similar type of bee exactly ten days previously.

Aspirin as a Local Analgesic

Dr. S. HILLMAN (Glasgow) writes: I should like to remind Dr. G. Sclare (December 10, p. 1352) that the insertion of a crushed aspirin into a tooth socket after painful extraction gives real relief. This, in addition to Dr. T. Anderson's reference in his article on the acute throat (October 15, p. 860), adequately illustrates the action of aspirin as a local analgesic.

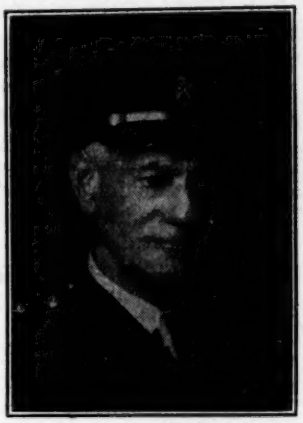
"Psychosurgery"

Dr. H. THISTLETHWAITE (Sedbergh) writes: I protest vehemently against the use of the word "psychosurgery." Unless you are prepared to equate "mind" (psyche) with "brain" (encephalon) the word can have no meaning. It has no etymological justification. Why could you not use the short, clear, English expression "brain surgery"?

Obituary

SIR CHARLES GORDON-WATSON, K.B.E., C.M.G F.R.C.S.

Sir Charles Gordon-Watson, whose career was one of distinction in military and civil surgery, died at York on December 19 at the age of 75. Before qualifying in 1898 he had enlisted at the age of 20 in the old Volunteers, and afterwards served in the Territorials. In 1899 he went out to the South African war, where he served until 1901 as a civil surgeon in the field force, gaining the medal and three clasps. At No. 1 Field Hospital he was associated with Sir Anthony Bowlby and Dr. Howard Tooth, two seniors from his own school, St. Bartholomew's. In the war of 1914–18 he began his service at the First London General Hospital, and then went to France. There he was in command of the Duchess of Westminster's hospital at Le Touquet. Later, with the rank of colonel, he was consulting surgeon to the Second Army, and afterwards to the British Army in Italy. In the war which began in 1939 he was made consulting surgeon to the British Army at home, and in 1943 he was promoted major-general.



[Russell, London

Charles Gordon-Watson was born in April, 1874, the son of the Rev. Henry George Watson, sometime vicar of St. Leonard's, Buckinghamshire He took the prefix "Gordon" by deed poll in 1920. He was educated at St. Mark's, Windsor, and at St. Bartholomew's Hospital. His service in South Africa followed a period as house-surgeon at his teaching hospital and at the Norfolk and Norwich Hospital. By the time he returned he had chosen general surgery as his career, and he obtained the F.R.C.S. in 1902. He was elected assistant surgeon to St. Bartholomew's in February, 1910, and later became joint lecturer in surgery to the medical school. Other appointments which he held were those of surgeon to St. Mark's Hospital, City Road, to the Metropolitan Hospital, and to St. Andrew's Hospital, Dollis Hill. He remained surgeon to St. Bartholomew's until his retirement under the age limit, when he became consulting surgeon.

In his early days Charles Gordon-Watson was specially interested in orthopaedics, and he collaborated with Howard Marsh in 1910 in the preparation of a new and enlarged edition of *Diseases of the Joints and Spine*, which Marsh had originally published fifteen years earlier. He also contributed articles on this subject to Latham and English's *System of Treatment*. Later he developed an interest in proctology. He was president of the Subsection of Proctology of the Royal Society of Medicine, and often took part in its discussions. He was also the author of the article on diseases of the rectum in Gask and Wilson's *Surgery*. Gordon-Watson served on the council of the Royal College of Surgeons from 1933 to 1940, and in 1937 he was Bradshaw lecturer. He also represented the College on the scientific advisory committee of the Radium Institute and Mount Vernon Hospital, of which committee he was vice-president. In 1931 he was made an Honorary

Fellow of the American College of Surgeons. He was a president of the Aesculapian Society and a member of the British Medical Association, to which he gave some useful assistance at the time—about 1931—when the Association was considering the question of patenting in the medical field. A body with which he was prominently identified for many years was the British Empire Cancer Campaign. He was a member of its executive and chairman of its investigation committee.

Gordon-Watson had an acute and inquiring mind, and never allowed the military cadre within which he worked for so many years to depress his initiative. In 1914 he made what was probably the first observation on trench frost-bite, on the basis of a number of cases admitted to the hospital in France of which he had charge. His military experience made him a strong advocate of the use of "bipp" (a dressing composed of bismuth, iodoform, and petrolatum), which he employed from an early stage of the last war.

To his many fine qualities of head and hand which made him an outstanding surgeon he added a manner of great charm and friendliness which must have been in many trying times a source of encouragement to his colleagues and of reassurance to his patients. At the Bath and Garrick and other London clubs, or on the golf links at Sandwich, he was an admirable companion. During the South African war he formed, with the late Sir Francis Fremantle, the South African civil surgeons dinner, which was held annually for many years. He was made a C.M.G. in 1916, and was knighted in 1919.

We are indebted to Mr. Reginald M. Vick for the following appreciation:

It must sometimes happen that the ordered details of a man's life fail to give an adequate picture of the man himself, and most certainly this is true of someone of the calibre of Gordon-Watson. His vivid personality, his untiring energy, his capacity for friendship, and his earnest desire to help others made him stand out among his fellows. Whatever he undertook he did with abounding enthusiasm. He was very keen on nearly all forms of recreation. As a young man he was a pioneer among motor-cyclists, and on more than one occasion he took part in the annual motor-cycle race from London to Edinburgh and back at a time when these machines were both novel and unreliable. Often I have ridden in the Row with him in the early hours of a summer's day, and I recollect one occasion when he was warned for exceeding the speed limit on his spirited mount. He was a most strenuous golfer and an incredibly energetic tennis player. At Bart's, as a student, he played soccer. In later years his interest lay in watching rugger, and I know that he always rather regretted that he had never taken part in the titanic struggles for the Inter-hospital Rugger Cup. He was one of the first members of the Bart's staff to drive a motor-car, and to ride with him in those early days of motoring was not without its thrills. In later life he took up horse racing and became a familiar figure on many a race-course.

When wars came, Gordon-Watson was always to the fore. He went as a very young man to the South African War. In the 1914–18 war he commanded the Duchess of Westminster's Hospital for Officers at Le Touquet, where his surgical skill and powers of organization had full play. He later became consulting surgeon to the Forces in Italy. In the recent war he once more became consulting surgeon to the Forces, which post he held until 1942.

As a teacher he shunned routine methods and taught with originality. As he grew older he spoke with the sure voice of a great experience. In surgery, his outstanding characteristic was courage. There was no operation too extensive for him to refuse to undertake, and he had some wonderful results. In dealing with carcinoma of the colon and rectum, which might be described as his specialty—although he remained a general surgeon to the end of his time—he always believed that it was right to tackle all cases where surgery offered any chance of cure. Needless to say, he had many disappointments, and I have known him to lose heart, but he always recovered rapidly and fought on. He was one of the first surgeons in this country to treat carcinoma of the rectum with radium. As is well known, this method proved a failure in many instances, but he saw to it that it had a full and fair trial. For a long period he treated suitable cases of this disease by the more conservative method of perineal resection, arguing, as was true in those days, that this operation was justifiable because of its lower mortality. Later he used to carry out the abdomino-perineal operation with considerable success. He was always a front-rank fighter in the battle against cancer, and took an active part in organizing research in that field.

One of Gordon-Watson's other lines was traumatic surgery in the days before all fractures automatically passed into the hands of the orthopaedic surgeons. He achieved excellent results with them, largely because of his mechanical turn of mind, which was well known to all who worked with him. He was an advocate of the Balkan beam, and was, I believe, the first surgeon (at Bart's) to affix the beam to a bed. His arrangement was somewhat primitive, but it was the precursor of the complicated fracture beds that we know now.

In his heyday Gordon-Watson had a very large private practice. To assist him at the hospital taught one a great deal, but to work with him in the more difficult surroundings of private practice was a liberal education indeed. He was always keenly interested in students' affairs, and was at one time or another either president or vice-president of many students' clubs. He took his duties seriously and regularly turned up at matches.

I had the privilege of living with him for many years in his house in Harley Street. The household consisted of four bachelors; in those spacious days entertaining on a large scale was the fashion, and it was indeed a gay bachelor establishment. Gordon married late in life, and he and Lady Gordon-Watson were absolutely devoted to one another. It might be said with truth that he never really recovered from the strain of her long and distressing illness, which ended with her death after they had been together for eighteen years. His son Michael now commands the 1st Battalion of the Scots Guards. Gordon-Watson had to undergo a major operation himself towards the end of his life, from which he made a wonderful recovery and came up smiling.

Gordon-Watson made many friends and held them, and there will be many to mourn him. He was always ready with a helping hand towards all those who worked with him. Generation after generation of chief assistants—many of whom are well-known surgeons to-day—house-surgeons, and dressers will bear witness to this splendid spirit in him. One of the most striking things about him was his delightful smile, which truly lit up his face. By his death another famous Bart's man—a great pioneer surgeon and a loyal friend—has passed on his way.

LANCELOT BROMLEY, M.Ch., F.R.C.S.

The sudden and unexpected death of Lancelot Bromley on December 17 at Seaford, Sussex, came as a great shock to his friends, by whom he had always been regarded as the personification of perfect health and physical fitness. The son of Sir John Bromley, he was born in London in

February, 1885. He received his early education at St. Paul's School, where he was captain of the cricket eleven and showed great proficiency as a gymnast. From school he went to Caius College, Cambridge. He played golf for the university and cricket and hockey for his college. He took his B.A. with honours in 1906, and began then his thirty-six years' association with Guy's Hospital. He qualified in 1909, took his F.R.C.S. in 1912, and the M.Ch., Cambridge in 1913.

Bromley made his mark as house-surgeon to Sir Alfred Fripp, and in 1911 he was appointed surgical registrar. He was an excellent teacher, who taught on the patients and not on the textbook description of their diseases. He was warden of the college from 1912 to 1919. In 1914 he married Dora Ridgway Lee, sister of the late Harry Lee, the ophthalmic surgeon of Leeds, who was his contemporary at Guy's Hospital. He was successively demonstrator of anatomy, deputy resident surgical officer, and dean of the medical school. Then in July, 1916, he was appointed assistant surgeon to Guy's. Bromley served in the R.A.M.C. from 1916 to 1918 in Salonika and Italy. On his return he was also appointed surgeon to the Surbiton and Putney Hospitals. It was at these latter hospitals that his ungrudging attendance at all times did so much to develop the scope and usefulness of the surgical service to the patients and their general practitioners. As a result he built up a large practice which continued until his retirement in 1946. In 1942 he resigned from the staff of Guy's in order to continue his work at the Ministry of Pensions Hospital at Stoke Mandeville, where he enjoyed working for ex-Service men—mostly naval ratings. For twenty years he was examiner in surgery at Cambridge, and found much pleasure in these visits to his old university.

His shy, modest, unassuming but helpful character gained for Lancelot Bromley the name of "Daddy," by which he was known to his intimates for over forty years. He had the happy knack of managing his life so well that he was able to combine a busy and successful surgical career with time somehow to satisfy his love of sport, especially golf, racing, yachting, and ski-ing. All these activities were carried out with his family, with whom he spent all his leisure. He was essentially a clinician with a sound knowledge of living pathology and a careful and tender craftsman. He wrote but little, because such time as he may have had for writing was devoted to his wife, children, and three grandsons. His elder son, John, a glider pilot, was killed on D Day near Caen. His daughter is the wife of Dr. R. A. P. Hogbin, a former Guy's rugby captain. His younger son is also a surgeon. As "Daddy" would readily have agreed, he owed his happiness and much of his success in life to the loving and tender care of his wife Dora, to whom all his colleagues and friends will extend sincere sympathy in her great loss.—W. E. T.

W. K. McKINSTRY, M.R.C.S.

Dr. William Kilbourn McKinstry died on December 7 at the early age of 50, after a short illness. The only son of Dr. W. H. McKinstry, now of Brighton and at one time pathologist to the Royal Northern Hospital, he was educated at St. Paul's School and Emmanuel College, Cambridge. McKinstry received his medical education at St. Bartholomew's Hospital and qualified in 1925. After qualification he was R.M.O. at the Westminster Hospital, where he had also been house-surgeon to the ear, nose, and throat and eye departments. He was later a house-physician at the Brompton Hospital.

While at the Westminster Hospital McKinstry had started to take an interest in anaesthetics, and he succeeded, while carrying on a busy general practice in West Kensington, in establishing himself in this specialty. In 1929 he was appointed honorary anaesthetist at the West London Hospital, a post he held until his death. He was also anaesthetist to the National Dental Hospital, and he had served, too, the Victoria Hospital for Children and the Royal Dental Hospital. During the recent war he was anaesthetist to the Royal National Orthopaedic Hospital. It is probable, however, that McKinstry's name will be best remembered in the realm of general practice, for he was in the best sense of the word a "family" doctor. Good-looking and with delightful manners, he was soon on friendly terms with new patients, while by his old ones he was considered a family friend, counsellor, and, if necessary, arbitrator. At his memorial service at St. Paul's, Knightsbridge, the writer overheard an elderly man say, "I feel like a ship without an anchor." His friends and colleagues will mourn the untimely death of an always genial and helpful companion.

He leaves a widow, herself a doctor's daughter, and two young daughters. The expressions of sorrow and loss from all his colleagues, patients, and friends may help a little to mitigate for them the tragedy which has overcome a particularly united and happy family.—O. L. C. S.

Mr. Alex. E. Roche, writes: W. K. McKinstry was a friend of very long standing. We went to the same preparatory and public schools, the same university, and the same hospital, and were subsequently close colleagues at another hospital, he being my anaesthetist, and an excellent one at that, and always calm and unruffled. One was completely confident if "Mac" was at the head end. Another, and an astonishing, coincidence is that we married on the same day of the same month of the same year. He was most sane and level headed, and an excellent man from whom to seek advice. He radiated vitality, cheerfulness, and kindliness, and one feels permanently enriched by his friendship. The rapidity and tragedy of his sudden illness leave one stunned, but he was so full of life that he is, and will always remain, vividly present to the memory of those who knew him.

Dr. Redvers Ironside writes: Others may testify to the professional abilities of William Kilbourn McKinstry and his skill as an anaesthetist. May a word or two be added about the loss his friends and colleagues have sustained by his premature death in the fullness of a happy and busy life. He was incapable of an uncharitable thought or deed, utterly unselfish in his work, and with a wonderful quality of imparting cheerfulness and joy to others. His courage and cheerful fortitude in his last illness were an example to those few who were privileged to be with him towards the end. "To live in the hearts of those we leave behind is not to die," and we who mourn his passing will always feel the cheerful, kindly warmth of his personality in remembering him.

J. C. writes: If the men who were boys when I was a boy could sit and drink with me, W. K. McKinstry would be my choice as chairman of that bright band. Years ago we used to meet on Saturday nights at the University of London Union in Malet Street. He was all that a Cambridge man should be: kind, urbane, grave or gay as the occasion demanded. Even then he had acquired that deep wisdom which bids man to be an artist of life: to appreciate folly in season. His death, as it were, snaps the last link in my chain of living reminders of the long days of youth.

Dr. MINA LOUISA DOBBIE died in a nursing-home in Bournemouth on November 23. She was the third daughter of Dr. Robert Dobbie, medical officer of health and general practitioner of Ayr, who died of typhus when she was a girl. She decided to take up medicine early in life, and studied at the London School of Medicine, the Royal Free Hospital, and later in Ireland. After qualifying she was a medical officer at the Crichton Royal Hospital. She became interested in remedial gymnastics and gymnastics for women, and was a pioneer in this field, going to Sweden to study their methods and translating the current Swedish textbook on the subject. She was a close friend and collaborator of the founder of the Chelsea Physical Training School, and was their medical officer for many years. She was also medical officer of the Aske's Haberdashers Girls' School at Acton and New Cross; also of the Maria Grey Training College at Brondesbury. She started general practice in Haverstock Hill, Hampstead, in 1899. She was an active member of the Hampstead Division of the B.M.A. for many years.

Dr. JAMES KIRKWOOD DUNLOP died at Sanquhar on November 24 at the age of 65 He was educated at Kilmarnock Academy, and graduated M.A. in 1905 and M.B., Ch.B. in 1908 at Glasgow University. After a year's assistantship with Dr. Roger in Sanquhar he spent a year as a house-surgeon in the Western Infirmary, Glasgow. He then returned to Sanquhar and continued to practise there until his retirement in June of this year. He was known to everyone in Upper Nithsdale, and when he retired he was presented with an illuminated address as a token of appreciation and respect. He was in every sense the family doctor, and there are few homes in the district where his passing has not meant the loss of a friend. Interested in the community as well as the individual, he served for ten years on the local town council. He was a keen supporter of the British Medical Association, and was chairman of the Dumfries and Galloway Division in 1945–6. While a student he was a keen golfer, and he maintained his interest in the game until ill-health compelled him to stop. For the last few years of his life he suffered from angina, but carried on his practice as he had always done, unselfishly and without counting the cost. Unfortunately, he was able to enjoy only six months' retirement. He is survived by his widow and two sons, to whom his colleagues and friends will extend their sympathy.—J. W.

Dr. THEODORE OGG died at his home in Hampstead, London, on December 5 after a short illness. Born at Fyvie, Aberdeenshire, in 1873, he was educated at Robert Gordon's College, Aberdeen, and at Aberdeen and Edinburgh Universities. As a student he won first prize in obstetrics and gynaecology at the Royal College of Surgeons, Edinburgh, where he later became demonstrator in midwifery. He took the Scottish triple qualification in 1897, and, after practising at Jarrow-on-Tyne and at Rothes, in Morayshire, for a time, he acquired an extensive practice at Huntly, Aberdeenshire. There he was honorary medical officer to the memorial hospital, where he undertook a fair amount of major surgery. He was asked by the Ministry of Pensions after the first world war to form a hospital for the treatment of disabled men from five northern counties. Later, following two years of special postgraduate study at Edinburgh and at Lausanne, where he took an M.D. in 1930, Dr. Ogg came to London. He was clinical assistant to the Soho Hospital for Women, and later physician to the Charterhouse Rheumatism Clinic. He was also medical officer to the Royal Sailors Daughters' School and Home at Hampstead. Dr. Ogg wrote a number of papers on rheumatism and on gynaecological and other subjects. An able diagnostician, he was very conscientious in his work, and endeared himself to his patients by his sympathy and kindness. He is survived by one daughter.

Dr. L. Carlyle Lyon writes: It is with a sense of more than usual regret that I, one of his grateful Aberdeen students of the years 1922–7, read (December 17, p. 1418) of the sudden death on November 29 of Mr. William Anderson, or "Willie," as he was invariably affectionately referred to by us all. As he hurried away after our 1927 Class Reunion Dinner, held in London on March 26 of this year, none of us present could have imagined from his vigorous, though tired, appearance that he would not live to see the New Year. His clinics in the old Aberdeen Royal Infirmary at Woolmanhill, and in the surgical out-patient department across the road, were an example of how medical students should be taught. His kindly handling of patients, putting them at their ease by his spontaneous and friendly use of the native dialect, as well as his consideration for the naïveté of the surgical beginner and his courtesy to the nursing staff, endeared him to all around him. His clinics were therefore always overcrowded, and there was invariably a rush by the more enthusiastic students to be amongst the early arrivals. His lectures on systematic surgery at Marischal College were a model of clarity and lucidity, and a pleasure to attend; while his surgical technique when he was operating was masterly. His place cannot readily be filled, and those of us who worked under him will always be indebted to him. One hopes there will be some fitting memorial erected to William Anderson in his old teaching school.

Dr. C. F. Ross writes: It does not seem long ago since we were giving a tea-party in the lab. for Leslie Humphrey (December 24, p. 1478) on his leaving us to join the R.A.M.C. Our chief had concluded a short speech with the words: "I am certain that Dr. Humphrey will make his mark in medicine." How sad it is to think that he was not to be spared to that end—to be cut off so near the beginning. Yet he seemed to have crowded into his short lifetime an amount of experience which some of us may never achieve. Knowing full well the eventual outcome of his illness, his constant solicitude for others shone to the end through the pain and blindness which he bore with such steadfast courage for so many months. Self-pity was entirely alien to his nature. Visits to him in hospital were not so much a consolation to the patient as a privilege to oneself, in making the most of all too fleeting a contact with his mind, too rare to be missed. The triumph of this mind over his body was exemplified in his behaviour, and will be an everlasting inspiration to those who had the honour to witness it. To his wife, whose perfect love and understanding must have given him infinite help in those last dark months, and to his two children, heartfelt sympathy goes out in abundance.

Medico-Legal

ADDICTION TO TRICHLORETHYLENE

At the Birmingham Assizes, on December 12, Mr. Justice Lynskey passed sentence on a man who was said to have killed his mother while under the influence of trichlorethylene, a drug to which he had become addicted.[1] Accepting a plea of not guilty of murder, but guilty of manslaughter, Mr. Justice Lynskey sentenced Peter Edwin Whillier, aged 26, of King's Heath, Birmingham, to five years' imprisonment.

For the prosecution Mr. Arthur Ward, K.C., said it would be difficult to prove intent at the time of the attack and therefore the prosecution was willing to accept this plea. Whillier had been employed at a power station near Birmingham where trichlorethylene was in use. He had got into the habit of soaking his handkerchief in trichlorethylene and inhaling the fumes. He was normally devoted to his mother, but on returning home after working a night shift he attacked her, and she died in hospital from a fractured skull.

Mr. Fearnley Whittingstall, K.C., who defended Whillier, said that he would have been able to call two doctors who would have given evidence that at the time of attack Whillier was in a state of delirium corresponding to that seen occasionally in people coming out of an anaesthetic. He was lashing out wildly without any control whatever.

[1] *Manchester Guardian*, December 13, 1949.

Medical Notes in Parliament

The King's Speech proroguing Parliament on December 16 made no reference to public health or to the passage of the National Health Service (Amendment) Act.

DEBATE ON NUTRITION

On December 15 Mrs. GANLEY opened a debate on nutrition. She commended the Government for continuing rationing, thus securing fair shares for all. She recalled that a leading French specialist had said in 1948 that in ten years England would have a generation of young men and women superior physically and mentally to that of any other European country. He was convinced that the excellent condition of these children was due to their feeding; their diet was perfectly balanced.

Viscountess DAVIDSON said that she had talked recently with two Australian doctors who had come back to this country for the first time since the war. They were deeply distressed at what they saw, particularly the appearance of the ordinary housewife. To produce more in the factories on a diet which only just reached the level of pre-war in quantity, but certainly not in quality, was impossible.

Mr. SOMERVILLE HASTINGS said there was a world shortage of food. Britain must take account of the needs of other countries and not demand more than a fair share of world supplies. In Britain about one-fifth of the people now received less food than before the war, about two-fifths received about the same, but the remaining two-fifths received much more food. He did not forget that there was a high incidence of tuberculosis, but this was probably due to the fact that the disease was more frequently recognized than before the war. There was no clear evidence that the death rate from tuberculosis was increasing. This death rate was the important guide to the nutrition of the people. He was a little unhappy, however, about the consumption of vitamins and fats. The fats the public now obtained were some some 16% below pre-war.

Colonel STODDART-SCOTT remarked that one could not get nourishment out of calories any more than out of a tape machine. What was nourishing was a balanced diet. Over many years this country had developed a diet suitable to its climatic conditions and industrialization. If the country was to get a more nourishing and attractive diet it must get more meat, more animal fats, and more animal proteins. He hoped consideration would be given to the question of food-poisoning. The handling of food was better than in the past and there were more refrigerators, yet the country never had so much food-poisoning as at present. He was sure that if Parliament got rid of rationing, nutrition and the health of the people would improve.

Dr. HADEN GUEST said that within a few years young people would look back on the medical reports of school doctors before the war and on Mr. Seebohm Rowntree's book, *Poverty and Progress*, almost as fairy tales. These conditions might return if food rationing was abolished. The nation was living at a very high standard of nutrition; rationing, price control, and subsidies were necessary to maintain that standard.

Tuberculosis and Nutrition

Mr. WALTER ELLIOT said that in Western Europe in the post-war years there had been a striking recovery in respect of many forms of illness, particularly tuberculosis. The Milroy Lectures, published recently in the *British Medical Journal* (November 12, p. 1065, and November 19, p. 1135), showed a remarkable clearing up of tuberculosis in Europe since 1921. In the years around 1947 the fall in France had been most spectacular. Since 1941 tuberculosis death rates in England and Wales had declined but did not reach the level which had been expected if pre-war trends had been continued. Scotland was the one country which showed no improvement since the end of the war. The trend there actually brought the tuberculosis rate in recent years above the worst period of 1930–1. The death rate from tuberculosis in 1946 in Scotland was 27, in Amsterdam 51, in Copenhagen 44, and in Stockholm 56. In Dundee it had gone up from 82 to 87. If progress was to continue Parliament must see that a more varied diet was available, moving towards the traditional high protein, big meat ration and not depending so much on the large starch ration.

Dr. EDITH SUMMERSKILL said that Mr. Elliot had failed to be objective. She contrasted his speech with his presidential address to the Royal Institute of Public Health and Hygiene published in the *British Medical Journal* (August 6, p. 297). The *British Medical Journal* had headed that address "Tuberculosis: Certain Unexplained Mortality Figures," whereas Mr Elliot had advanced in the present debate an argument trying to prove that the high tuberculosis rates in Scotland could be attributed to the nutritional policy of the Labour Government.

She said that some newspapers had confused averages with specific allocations in discussing rations. If the calorie consumption averaged 3,000 a day and a small child only required a few hundred calories, the heavy workers were consuming something like 4,500 calories. On sugar Dr. Summerskill said there had been a slight increase in consumption but the Government had not the dollars with which to pay for more sugar from Cuba. As for meat, the Ministry of Food had a representative in every meat-producing country who was trying to find available meat supplies. The consumption of milk was 55% greater than before the war and had steadily increased since 1940. A further improvement was expected in 1950. In the present year the Minister of Food had decided to carry out a survey of approximately 2,400 households representative of all economic classes. In this study, made in May, 1949, when milk was unrestricted, the Ministry discovered that the consumption of milk was between 6 pints and 4¼ pints per head per week, against 5.4 pints in the highest income groups in the 1930's and 1.1 pints in the lowest income group.

She would like to see more fats available, but a clinical survey had shown no sign of there being a fat deficiency in this country. In 1947 the supply of fats was something like 75% of pre-war, but for the whole of 1949 it was 98% of pre-war. It was good to have margarine fortified with vitamins A and D, and the margarine of to-day was infinitely superior to the yellow grease used years ago. Of flour consumption 19% had been replaced since July, 1949, by the extra fats now available. This was a transfer of 60 calories a day.

The most spectacular change in the public health of the country was the almost complete elimination of rickets. At the beginning of the century one-third of the London children had rickets. Now it was possible to walk down a London street and not see one pair of bandy legs or knock-knees. Cure and prevention of rickets was by means of cod-liver oil, which was now distributed free. The Government was not withholding any of these important nutrients from the poorest income groups. Wise feeding was one of the greatest weapons that preventive medicine could wield, and she looked forward to the day when the Ministry of Food could allocate a balanced diet with a full complement of every nutrient without having to consider the supply question.

The report of the Chief Inspector of Mines for the year 1947 has recently been issued (H.M.S.O., price 1s. 3d.). It describes how "beat" diseases account for the largest number of cases of industrial disease in miners at the present time. The incidence of "beat knee" has risen gradually over the past 10 years, and this increase is believed to be due to the growing use of conveyers in the thinner seams. The ideal knee-pad, which will exclude the accumulation of small particles between the pad and the knee, has yet to be designed. Pneumoconiosis continues to be the most important cause of wastage of manpower. The highest incidence is in the South Wales coalfield, but the number of certified cases there has fallen from a peak figure of 5,821 in 1945 to some 3,800 cases in 1947. In the other coalfields of Great Britain there has been an increase from 597 cases in 1945 to some 950 cases in 1947. The report also points out that the number of recorded cases of miners' nystagmus is almost the same to-day as it was ten years ago.

Universities and Colleges

UNIVERSITY OF EDINBURGH

The following medical degrees and diplomas were conferred at a Graduation Ceremonial held on December 16:

M.D.—[1]A. K. Bannister, J. B. Borthwick, D. P. Degenhardt, [1 2]G. W. A. Dick, [4]Rose I. L. Donaldson, [2]J. P. Duguid, [1]D. E. P. Forbes, [1 4]Constance C. Forsyth, [4]I. C. Gilliland, S. H. Graham, [4]A. F. Maccabe, [4]I. A. G. MacQueen, [4]I. C. Monro, M. B. O'Neill, [4]J. B. Wilson.

PH.D.—In the Faculty of Medicine: [1]R. A. Miller, M.D., F.R.C.P.Ed.

M.B., CH.B.—Nancy M. Adams, D. J. M. Allan, T. D. Bleakley, N. T. D. Brewis, J. D. Campbell, I. P. Dunnett, Mary B. Edwards, T. W. G. Fraser, J. H. Greig, C. J. Hardie, D. C. Hudson, Mary E. R. Hughes (née Latimer), Anne E. Jameson, J. D. Litt, Mary B. B. McGregor, A. J. H. MacLennan, J. H. McMillan, D. M. McNab, Margery Matheson (née Dunn), R. D. Merson, P. A. Metcalfe, J. G. Mitchell, R. S. H. Pasqual, D. E. Ryder, I. M. Simpson, Pansy E. Smith, Joyce Stirling, Margaret A. Tait, A. Taylor, Jessie J. F. Tennent, Janet I. Thompson, P. G. W. Weston, T. A. White, Marjorie N. P. Whyte, J. R. Wilson, Sybil M. D. Wood.

D.P.H.—Ewe Hin Ong.

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—E. A. Keith, W. Macleod.

DIPLOMA IN MEDICAL RADIOTHERAPY.—A. Henderson, K. S. Mowatt, J. D. Sammon, V. K. Sundaram.

[1]In absentia. [2]Awarded medal for thesis. [3]Highly commended for thesis. [4]Commended for thesis.

UNIVERSITY OF DURHAM

The following medical degrees were conferred in Congregation on December 16:

M.B., B.S.—J. T. Clow, Evelyn C. Cummings, J. M. Finnerty, J. Hayes, Sheila Hedley, A. B. C. Hotobah-During, J. Kirkup, J. McHugh, T. A. O'Sullivan, N. G. Pearson, J. W. Salkeld, W. Shaw, T. Silver, L. B. Strang, E. J. Thomas, D. Veitch, Margaret C. Watkinson, B. H. Webb, D. Webster, R. Williams, *W. D. Baston.

*In absentia.

UNIVERSITY OF BIRMINGHAM

The following appointments have been made: Dr. J. C. Bowie, representative of the University at the Health Congress of the Royal Sanitary Institute, Eastbourne, April, 1950; Mr. S. D. Loxton, Lecturer in Obstetrics and Gynaecology, from December 1, 1949; Dr. E. C. Fox, Lecturer in Operative Dental Surgery, from January 1, 1950.

The title of Honorary Research Fellow in the Department of Physiology has been conferred on Mrs. M. Beznak, M.D.

UNIVERSITY OF LEEDS

At a meeting of the University Court held on December 21 it was decided to confer the honorary degree of D.Sc. on William Norman Pickles, M.D., M.R.C.P., medical officer of health for the Aysgarth Rural District Council, at a Congregation to be held on May 19, 1950.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a meeting of the Royal College of Surgeons of Edinburgh held on December 14, 1949, with Mr. W. Quarry Wood, President, in the chair, the following candidates, having passed the requisite examinations, were admitted Fellows: N. R. Butcher, J. C. Campbell, B. S. Dhillon, K. MacD. Douglas, R B. Duncan, R. Fahmy, J. R. Hutchinson, W. S. Johnston, I. Lindsay, R. C. R. Loane, W. C. Lloyd-Smith, W. C. Menzies, J. A. Mitchell, A. L. Morton, K. Prasad, P. L. Rishi, D. E. Robertson, Dorothy E. Rowling, P. N. Simons, I. S. R. Sinclair, B. P. Singh, Z. H. Y. Sobani, A. G. M. Watt.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

Dr. William J. Dieckmann, Director of the Department of Obstetrics and Gynaecology, Chicago Lying-in Hospital, will deliver a lecture on "The Aetiology of Pre-eclampsia—Eclampsia" at the College House (58, Queen Anne Street, London, W.) on Wednesday, January 11, at 5 p.m. Fellows and Members of the College and other medical practitioners interested in the subject are invited to attend the lecture, admission to which is by ticket only, obtainable from the secretary of the College.

Medical News

Crown Representative on G.M.C.

Sir Henry Cohen has been reappointed Crown Representative on the G.M.C. for the term of five years from January 24, 1950. He was first appointed Crown Representative five years ago.

Elastic Adhesive Bandages B.P.C.

The Ministry of Health states that production of one of the two packs of these bandages hitherto in use will be discontinued from January 1, 1950. After that date stocks of the carton "N.H.S." pack may be dispensed where elastic adhesive bandage is ordered on Form E.C.10 while supplies of this pack are being exhausted. The carton pack is being replaced by a pack in tin containers labelled "Elastic Adhesive Bandage B.P.C." Since this pack may be the pack adopted by manufacturers for their branded product, the respective brand name or trade mark of the manufacturer may also appear on the tin. The prices included in the January Drug Tariff for the two widths of this bandage will be the prices for the new tin pack. Whether the carton or the tin pack has been dispensed, these prices will be paid until April 1, after which date the bandage in the tin container only may be dispensed against orders on Form E.C.10. For diachylon base bandages the tin container will be of distinctive colour.

Enjoying Health

How to achieve health and enjoy it is the theme of a pamphlet by Dr. Charles Hill entitled "Health and the Family" (Conservative Political Centre, 1s.). Writing for the lay reader, he discusses the importance to health of a happy home and good conditions of work, and makes some suggestions on such topics as the care of old people and the design of houses. "Men are not changed by legislation," he says, and he gives them plenty of homely advice that will doubtless be more helpful.

Guild of St. Luke

The annual meeting of Catholic doctors of the Guild of St. Luke, SS. Cosmas and Damian was held on December 18 at the Hospital of St. John and St. Elizabeth, London. Dr. W. B. J. Pemberton was re-elected Master of the Guild, Dr. P. Corridan honorary treasurer, and Dr. W. J. O'Donovan honorary secretary. A memorandum setting out the considered opinion of the Guild on some matters raised in the Royal Commission's Report on Population was the chief business discussed at the meeting.

Whooping-cough Research

Dr. Pearl Kendrick, of the Michigan Department of Health, is in London discussing whooping-cough vaccines with British research workers. According to a statement issued by the Medical Research Council, Dr. Kendrick has given valuable help with the investigations into whooping-cough vaccine being carried out in this country. She is discussing on the basis of her wide experience in the U.S.A. present and future trials of whooping-cough vaccine in Britain. Dr. Kendrick is a corresponding member of the Medical Research Council whooping-cough immunization committee, and is here under the auspices of the World Health Organization.

Consultant Psychiatrist to WHO

Dr. Lucien Bovet, chief of the Office Médico-Pédagogique of the Canton de Vaud at Lausanne, has been appointed consultant on juvenile delinquency to the World Health Organization. He will shortly tour Holland, Sweden, Finland, France, England, and the U.S.A.

Treatment of Anthrax, Botulism, and Snake-bite

Arrangements which are to operate from January 1, 1950, are being made for emergency supplies of sera for the treatment of anthrax, botulism, and snake-bite to be kept at the following centres. In each case the centre will maintain a twenty-four-hour service.

Centre	*Telephone Number*
The Dispensary, Newcastle General Hospital	Newcastle 35211
The Dispensary, Cumberland Infirmary, Carlisle	Carlisle 590
Seacroft Hospital, York Road, Leeds	Leeds 45194
Castle Hill Hospital, Cottingham, York	Cottingham 47372
Nottingham City Hospital, Hucknall Road, Nottingham	Nottingham 42554
Regional Blood Supply Depot, Brookland Avenue, Cambridge	
Monday to Friday, 8 a.m.–10 p.m. / Saturday 8 a.m.– 6 p.m.	Cambridge 2536
All other times	Cambridge 87988
North Middlesex Hospital	Tottenham 3071
South London Blood Supply Depot, Benhill Avenue, Sutton	Vigilant 0068
Northampton General Hospital	Northampton 4680
Royal Berkshire Hospital, Reading	Reading 2231
Ham Green Hospital, Bristol	Till 31165
Swilly Isolation Hospital, Plymouth	Plymouth 4311
Canton Infectious Diseases Hospital, Cardiff	Cardiff 960
Dudley Road Hospital, Birmingham	Northern 3801
The Dispensary, Manchester Royal Infirmary	Ardwick 3300
The Fazakerley Isolation Hospital, Liverpool	Aintree 2324

In addition, 10-ml. containers of anthrax antiserum for use *prophylactically* in persons exposed to infection may be obtained during the daytime from the following centres:

Public Health Laboratory, 16–18, Edmund Street, Bradford	Bradford 24314
Public Health Laboratory, 184, High Street, Kingston-upon-Hull	Hull 35371
Bacteriological Department, City Laboratories, 126, Mount Pleasant, Liverpool	Royal 3636
Central Public Health Laboratory, Colindale Avenue, London, N.W.9	Colindale 6041 and 4081
Public Health Laboratory, General Hospital, Westgate Road, Newcastle, 4	Newcastle 34920
Public Health Laboratory, General Hospital, Northampton	Northampton 347
Public Health Laboratory, County Hall, Taunton	Taunton 3451
Public Health Laboratory, Institute of Preventive Medicine, The Parade, Cardiff	Cardiff 8288

COMING EVENTS

Meeting of Registrars

All registrars in the North-west Metropolitan Region are invited to attend a General Meeting at B.M.A. House on Wednesday, January 4, at 4.30 p.m. The objects of the meeting are to elect a permanent committee and also three representatives to the Central Council of the Registrars Group of the B.M.A.

Alcoholism

A joint meeting of the Society for the Study of Addiction and the Section of Psychiatry of the Royal Society of Medicine will be held at 1, Wimpole Street, London, W., on Tuesday, January 10, at 8 p.m., when Dr. Erik Jacobsen, of Copenhagen, will read a paper on "Biochemical Methods in the Treatment of Alcoholism, with Special Reference to Antabuse." A discussion will follow.

Diet in Infancy and Childhood

A course of lectures for postgraduates on "Diet in Infancy and Childhood" will be delivered by members of the staff of the Institute of Child Health and visiting lecturers at the Hospital for Sick Children, Great Ormond Street, London, W.C., on Tuesdays, at 5 p.m., from January 17 to March 21, both dates inclusive. The fee for the course of ten lectures is £3 3s. Applications for tickets of admission (limited in number), accompanied by a remittance, should be sent to the secretary of the Institute of Child Health at the hospital.

Society for Endocrinology

The Society for Endocrinology has arranged a lecture on "The Nature of Adrenocorticotropic Hormone (ACTH)" to be given by Dr. C. H. Li (Institute of Experimental Biology, University of California, Berkeley, California) at the Royal Society of Medicine, 1, Wimpole Street, London, W., on Thursday, January 26, at 5 p.m. Admission is free, without ticket.

SOCIETIES AND LECTURES

Tuesday

INSTITUTE OF DERMATOLOGY, 5, Lisle Street, Leicester Square, London, W.C.—January 3, 5 p.m., "*Animal Diseases Communicable to Man*," by Dr. M. S. Thomson.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—January 3, 5 p.m., "*Tumours of the Kidney*." Erasmus Wilson Demonstration by Mr. C. E. Shattock.

Wednesday

LONDON COUNTY MEDICAL SOCIETY.—At St. Giles's Hospital, Camberwell, S.E., January 4, 3.15 p.m., annual general meeting, followed by an address by Dr. C. D. S. Agassiz.

Thursday

FACULTY OF HOMOEOPATHY.—At Royal London Homoeopathic Hospital, Great Ormond Street, London, W.C., January 5, 5 p.m., "*The Homoeopathic Treatment of Common Liver and Gall-bladder Disorders*," by Dr. E. K. Ledermann.

INSTITUTE OF DERMATOLOGY, 5, Lisle Street, Leicester Square, London, W.C.—January 5, 5 p.m., "*Eczema and/or Dermatitis*," by Dr. Brian Russell.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—January 5, 5 p.m., "*Injuries of the Nose and Sinuses*," Otolaryngology Lecture by Mr. Rainsford Mowlem.

ROYAL PHOTOGRAPHIC SOCIETY: MEDICAL GROUP.—At 16, Princes Gate, London, S.W., January 5, 7 p.m., "*Display Methods in Medical Illustration—Graphic and Photographic*," by Miss Sylvia Treadgold (Department of Medical Illustration, Guy's Hospital).

Friday

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—January 6, 5 p.m., "*Tumours of the Testicle*." Erasmus Wilson Demonstration by Mr. C. E. Shattock.

MAIDA VALE HOSPITAL MEDICAL SCHOOL, Maida Vale, London, W.—January 6, 5 p.m., Neurological Demonstration by Dr. Redvers Ironside.

Saturday

PHYSIOLOGICAL SOCIETY.—At Guy's Hospital (Physiological Laboratory), London, S.E., January 7, 11 a.m., demonstrations and communications.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Benjamin.—On December 18, 1949, at the London Hospital, E., to Astrid (née Persson) and Hugh Benjamin, M.B., F.R.C.S.Ed., F.R.F.P.S., of Johannesburg, a daughter

Harrison.—On December 15, 1949, at 10, Millington Road, Cambridge, to Mary (née Marryat), wife of G. Kent Harrison, F.R.C.S., a daughter.

Mellor.—On December 17, 1949, at the Buckingham Nursing Home, Leeds, to Jean Marie (née Walker Wood), wife of Norman Mellor, M.B., Ch.B., a son.

DEATHS

Boyd.—On December 17, 1949, at Blythe Bridge, Stoke-on-Trent, Staffs, Edmund Robert Boyd, M.B., Ch.B.

Bromley.—On December 17, 1949, at Seaford, Sussex, Lancelot Bromley, M.Ch., F.R.C.S.

Buckley.—On December 20, 1949, at Broadhurst, Bury, Old Road, Manchester, John Philip Buckley, M.S., F.R.C.S.

Cholmeley.—On December 17, 1949, at the Royal Hospital, Wolverhampton, William Frederick Cholmeley, F.R.C.S., aged 83.

Cope.—On December 17, 1949, at Marylands, Hilltop Crescent, Cosham, Portsmouth, Lidbrooke Frank Cope, O.B.E., L.S.A., Surgeon Captain R.N., retired.

Egan.—On December 17, 1949, at the London Hospital, E., William Egan, M.R.C.S., L.R.C.P., aged 52.

Gordon-Watson.—On December 19, 1949, at York, Sir Charles Gordon-Watson, K.B.E., C.M.G., F.R.C.S., Major-General, A.M.S.

Hirst.—On December 16, 1949, at Brompton Hospital, London, S.W., Henry Adamson Hirst, M.R.C.S., L.R.C.P., of Spa Grange, St. Helen's Road, Hastings, Sussex, aged 50.

Hutchinson.—On December 20, 1949, at The Cottage, Grammar School Lane, Northallerton, Yorks, Joseph Armstrong Hutchinson, M.D., aged 91.

McClure.—On December 17, 1949, at Edinburgh, Alexander Robert McClure, M.B., Ch.B., of Park House, Wellington, Shropshire, aged 57.

McGregor.—On December 18, 1949, in hospital, Aden, Donald McGregor, M.B., Ch.B., aged 49.

Morris.—On December 19, 1949, in Nairobi, Charles Sculthorpe Morris, M.R.C.S., L.R.C.P., I.D.S., of 77, Albert Hall Mansions, London, S.W., and formerly of 88, Park Street, London, W., aged 74.

Newton.—On December 20, 1949, at 14, Pentland Avenue, Colinton, Edinburgh, William Henry Newton, M.D., D.Sc.

Roberston.—On December 16, 1949, at Hamburg, Hamish Gordon Grant Robertson, M.R.C.S., L.R.C.P., D.P.H., Lieutenant-Colonel, R.A.M.C.

Rorie.—On December 16, 1949, at 41, Albyn Place, Aberdeen, Frank Miller Rorie, M.B., Ch.B., aged 54.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended December 10. [No. 49

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1949					1948 (Corresponding Week)				
	(a)	(b)	(c)	(d)	(e)	(a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	37	4	26	—	—	39	4	19	—	—
Deaths		2	—				2	—		
Diphtheria	87	7	37	3	1	144	12	45	7	9
Deaths	3	—	—	—	—	2	—	—	—	—
Dysentery	133	14	73	—	3	69	13	44	—	—
Deaths				—	—				—	—
Encephalitis lethargica, acute	—	—	—	—	—	—	—	—	—	—
Deaths		—					—			
Erysipelas			31	10	3			30	21	2
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				33					36	
Deaths	13	—	4	1	1	29	—	7	1	2
Measles*	1,596	26	22	89	119	10,094	176	147	51	63
Deaths†			—	—	—			—	—	—
Ophthalmia neonatorum	38	3	5	—	1	36	5	20	—	—
Deaths										
Paratyphoid fever	5	1	1 (B)	—	2 (B)	3	1	1 (B)	—	—
Deaths	—	—	—	—	—	—	—	—	—	—
Pneumonia, influenzal	734	26	12	1	11	1,027	81	9	1	6
Deaths (from influenza)‡	23	6	3	—	—	24	4	3	—	—
Pneumonia, primary			287	35				397	28	
Deaths	236	48		12	7	321	71		3	18
Polio-encephalitis, acute	10	—				1	—			
Deaths										
Poliomyelitis, acute	124	15	1	2	—	35	4	3	2	—
Deaths§	11	—				1	—			
Puerperal fever		—	5				—	8		—
Deaths										
Puerperal pyrexia‖	57	7	7	—	1	98	8	2	—	—
Deaths		—					—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	2,855	214	249	123	269	1,410	85	287	170	45
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	4	—	—	3	—	4	1	2	—	—
Deaths	1	—	—	—	—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Whooping-cough*	893	33	59	16	52	2,522	187	159	74	9
Deaths	—	—	—	—	—	13	1	3	—	—
Deaths (0–1 year)	263	37	42	16	11	360	54	60	13	7
Deaths (excluding still-births)	5,222	873	702	184	136	5,497	944	659	154	107
Annual death rate (per 1,000 persons living)			14·1	11·4				13·3	9·6	
Live births	6,595	1047	849	308	224	7,212	1220	867	303	227
Annual rate per 1,000 persons living			17·0	19·1				17·5	19·0	
Stillbirths	193	27	15			219	24	21		
Rate per 1,000 total births (including stillborn)			17					24		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

EPIDEMIOLOGICAL NOTES

Typhoid in a Liner

When the liner s.s. *Mooltan* arrived in the Port of London on December 16 three sick members of the crew were removed to hospital for observation. On subsequent days further members of the crew were admitted to hospital, and a diagnosis of typhoid fever has now been confirmed in some of them. On December 22 a total of 11 confirmed cases were under treatment, and 5 further members of the crew were under observation in hospital. The organism is Vi-phage type A. Retrospective inquiries suggest that the dates of onset of illness were during the last ten days of the voyage.

One passenger has been admitted to hospital as a suspected case of enteric fever. The names and addresses of passengers and members of the crew who left the vessel have been notified to medical officers of health of the destination to which they were proceeding.

Discussion of Table

In *England and Wales* there were falls in the notifications of whooping-cough 88, measles 58, dysentery 26, and acute poliomyelitis 17, while the only large rise was in the incidence of scarlet fever 100.

A small rise in the incidence of scarlet fever was reported from most areas; the largest increase was London 31. The notifications of measles remained almost constant in most counties; the exceptions were decreases in Durham 212 and Norfolk 83 and an increase in Lancashire of 110, mainly contributed by Liverpool C.B. with a rise from 77 to 145.

A small decrease in the incidence of whooping-cough was recorded in most areas; the only large fall was 47 in Yorkshire West Riding. The only marked change in the notifications of diphtheria was an increase of 8 in Staffordshire.

Two fresh outbreaks of dysentery were reported during the week, one affecting 24 persons in Berkshire, Wokingham R.D., and the other with 18 notifications in Staffordshire, Wolverhampton C.B. Only 2 cases were notified in Gloucestershire and in Cheshire; in the preceding week the notifications were 30 and 16, respectively. The other large returns for dysentery were Lancashire 21 (Preston C.B. 7, Liverpool C.B. 6); London 14 (Poplar 7); Northumberland 11 (Newcastle-upon-Tyne C.B. 9). The largest outbreak of food-poisoning was that in which 43 cases were notified in Wiltshire, Salisbury M.B.

In *Scotland* there were decreases in the notifications of acute primary pneumonia 63, scarlet fever 35, whooping-cough 23, and dysentery 21, with increases in the incidence of cerebrospinal fever 12 and diphtheria 8. The rise in the notifications of cerebrospinal fever and diphtheria was contributed by Glasgow. Notifications of dysentery came mainly from Glasgow 23 and Stirling county 15.

In *Eire* there were decreases in the notifications of scarlet fever 34 and whooping-cough 28. Notifications of diarrhoea and enteritis fell by 9 in Dublin C.B., but there was a rise of 14 in the rest of the country.

In *Northern Ireland* there were only small changes in the notifications of infectious diseases. In Belfast C.B. a decline of 31 was reported in the notifications of measles, but there was a rise of 34 in the remainder of the country.

Initial plans for the control of venereal disease in the South-east Asia Regional Organization of WHO are being drafted on the basis of reports furnished by Dr. George M. Leiby, WHO consultant working with the WHO regional office in New Delhi. The plan includes a project for the eradication of yaws in Indonesia. Unicef has allocated $700,000 to it. A scheme for controlling syphilis will be combined with it. Dr. Leiby, who is professor of internal medicine and syphilology at the University of California, will also visit Bangkok to discuss plans for V.D. control in Siam. It is believed that adequate V.D. services can be introduced in Ceylon in conjunction with the Mother and Child Welfare Organization there. After completing his tour of Burma and Indonesia, Dr. Leiby will be replaced by Dr. N. Jungalwalla, who will be the permanent consultant in venereal diseases to WHO in South-east Asia.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Control of Dust-borne Infection

Q.—*(a) How useful is the oiling of floors and blankets in preventing cross-infection? What oils should be applied, in what quantities, and how often? Can you mention any hospitals using the method now? (b) What is the best method of aerial disinfection? I take it that the only effective chemical available commercially is sodium hypochlorite?*

A.—(*a*) Dust in a hospital ward consists largely of particles of fabrics from the patients' beds; when these fabrics are contaminated by secretions or discharges the dust arising from them, and the air when dust is formed or disturbed as by bed-making or floor-sweeping, can be shown to contain surprisingly large numbers of pathogenic bacteria. That oiling, by causing such particles to stick together in indispersible masses, much reduces aerial contamination and actually reduces the amount of cross-infection has been fully proved. Papers which should be consulted are those of Thomas and Van den Ende (*Journal*, 1941, **1**, 953), Van den Ende and Thomas (*Lancet*, 1941, **2**, 755), Thomas (ibid., 1941, **2**, 123), Van den Ende, Edward, and Lush (ibid., 1941, **1**, 716), and Wright, Cruickshank, and Gunn (*Journal*, 1944, **1**, 611). These contain information about methods, which cannot be detailed here, as well as results. The oiling of floors is simple and inexpensive, and requires repetition only at intervals of three or four weeks; the treatment of blankets and garments is much more difficult and expensive and requires skilled laundry co-operation. The only present-day use of both processes of which we have knowledge is in the Burns Unit of the Birmingham Accident Hospital, although it may well be that other hospitals use them. The oiling of floors only has been continued at the L.C.C. North-Western Hospital (where the observations of Wright *et al.* quoted above were made), in the wards of the Facio-Maxillary Unit, Hill End Hospital, St. Albans, and doubtless elsewhere. It should perhaps be pointed out that this method of dealing with infected dust is only one of many precautions, some alternative to it, whereby the risks of cross-infection may be diminished.

(*b*) Most of the information asked for in this question can be found in the memorandum "Studies in Air Hygiene" (*Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 262, 1948), which was the subject of a leading article in the *Journal* for September 17, 1949 (p. 640). The best method of aerial disinfection depends on many circumstances not specified in the question. For temporary use in an emergency such as an air-borne epidemic, and in premises where elaborate installations employing ultra-violet light or glycol vapours are out of the question, it is true that sodium hypochlorite is the best agent available.

Sympathectomy for Intermittent Claudication

Q.—*What are the indications for sympathectomy in intermittent claudication? Is there any means of telling what is the state of the arteries at any time and at any level?*

A.—Recent investigations have shown that sympathectomy is of benefit in the milder degrees of intermittent claudication, where the pain either wears off or remains constant even with continued walking. In such cases a high proportion of patients can be greatly relieved by the operation, or by chemical destruction of the lumbar sympathetic chain by phenol injection, when open operation is contraindicated by the patient's age or general condition. In the more pronounced degrees, when further walking is prevented by the development of severe pain, only about one-third of cases obtain benefit from sympathectomy, and in this group the operation is hardly justifiable. Phenol injection can be tried, provided the patient understands that improvement is by no means certain. If this confers no benefit, tenotomy of the affected muscles should be considered, as this operation can greatly increase the walking distance.

Some indication of the degree of generalized arteriosclerosis can be obtained from estimation of the blood pressure and from palpation of the course and consistency of the brachial and radial arteries, while radiographs of the limbs show the degree of calcification in the arteries. The patency of the arteries at any level can be estimated by palpation of the pulses or by oscillometry, and the presence of other evidence of ischaemia, such as muscle-wasting and pallor of the foot on elevation or exercise. The exact state of the limb arteries can be demonstrated by arteriography, but clinical examination is usually sufficient to assess the extent of the ischaemia.

Subacute Combined Degeneration

Q.—*How should a case of subacute combined degeneration of the cord where the neurological symptoms are predominant be treated? One proprietary liver extract has been used, and discarded because it produced a dark-brown discoloration of the urine with a high specific gravity. Is there any explanation for this, as the urine is otherwise normal? How soon may improvement in the neurological signs and symptoms be expected with adequate dosage?*

A.—Subacute combined degeneration of the cord requires full and intensive treatment, and the doses of the anti-anaemic preparations used should not be reduced even when the blood count has returned to normal. If liver extracts are employed, then doses of 2–4 ml. intramuscularly daily for a fortnight or longer should be followed by similar doses on alternate days, and then two or three times weekly until the condition is much improved. With more concentrated or purified liver extracts, 1–2 ml. should be given at similar intervals. Good responses are obtained to the continued administration of 10 g. of desiccated pig's stomach thrice daily; this should be given in cold water or cold milk after meals and should not be heated. Sometimes in the early stages it is of advantage to combine parenteral liver and oral stomach therapy. Liquid liver extract or proteolysed liver in a dose of 1 oz. (28 ml.) twice daily may also be tried.

Recent investigations have suggested that vitamin B_{12} may be of value in the treatment of this condition, but as yet dosage and long-term effects have not been fully reported. Doses of 40–60 μg. intramuscularly once or twice weekly might be tried. Under no circumstances should folic acid be used, either alone or in combination with any other preparation. Ancillary treatments will include: (*a*) acid. hydrochlor. dil. 30 minims (1.8 ml.) and glycerin. pepsin. 1.5 dr. (5.25 ml.) in a tumblerful of water after each meal if there are any gastrointestinal symptoms; (*b*) supplementary vitamins, especially B complex, and also ascorbic acid (50 mg. three times a day); (*c*) a full normal diet; and (*d*) massage and exercises for the limbs. The response will vary according to the severity of the initial condition, the intensity and persistence of the treatment, and the individual sensitivity of the patient. Improvement should be noticeable in the first few weeks, particularly as the blood count returns to normal, after which it should be progressive although probably slow. Paraesthesiae and some spasticity may persist for a very long time.

A dark-brown urine is noted occasionally after the use of certain very crude preparations of liver, and is probably due to pigmentary matter extracted from the original liver tissue.

Treatment of Coronary Thrombosis

Q.—*What is the most satisfactory modern treatment of coronary thrombosis? Is heparin or dicoumarol of proved value?*

A.—The mortality rate of all cases of acute coronary thrombosis treated with rest alone is in the region of 20%. If an 800-calorie diet is maintained for the first week and a light diet thereafter the mortality rate drops to around 15%. The addition of anticoagulant therapy lowers it another 2½%, and practically abolishes thrombo-embolic complications such as cerebral thrombosis, phlebothrombosis, pulmonary infarction, and massive pulmonary embolism. The slight lowering of the

mortality rate may be fairly attributed to the absence of deaths from massive pulmonary embolism. It is likely, though not yet proved, that the administration of quinidine 3–5 gr. (0.2–0.32 g.) thrice daily for the first month may diminish the number of deaths from ventricular fibrillation. In other words, the combination of a low-calorie diet, anticoagulants, and quinidine may be expected to halve the mortality rate of acute coronary thrombosis. In practice it is usual to limit anticoagulants to those cases in which thrombo-embolic complications are likely. The criteria for employing such therapy include: (*a*) marked fall in blood pressure; (*b*) any evidence of left ventricular failure or congestive heart failure; (*c*) paroxysmal tachycardia or auricular fibrillation; (*d*) electrocardiographic signs indicating gross infarction—for example, monophasic Q waves and persistent elevation of the ST segment in left ventricular surface leads and their equivalents; and (*e*) any direct signs of thrombosis elsewhere. If heparin were easier to give and less expensive, or dicoumarol were less dangerous and required less laborious control, the anticoagulants would probably be given as a routine to all patients; but, as they are not, some selection is usual.

Pruritus During Pregnancy

Q.—*What is the best treatment for pruritus of pregnancy? A patient suffered considerably in her first two pregnancies; she is now two months pregnant and already the irritation has started in the vulva. There are no abnormal physical signs and the urine is free from sugar.*

A.—If the pruritus is limited to the vulva there is nearly always a local cause for it, and, even if there is no glycosuria and no obvious vaginal discharge, vaginal swabs should be repeatedly examined to exclude trichomonas and monilia infection. If all such local causes are excluded, treatment with acid. hydrochlor. dil. 30 minims (1.8 ml.) in a tumbler of water three or four times daily with meals may be tried tentatively. The cause of generalized pruritus associated with pregnancy is unknown, but the nature of the skin lesion rather suggests an allergic basis. Treatment is empirical, and, if antihistamine drugs are ineffectual, stilboestrol, 5 mg. thrice daily by mouth, sometimes seems to help. Calcium gluconate in large doses is also used. Frequent bathing with 1% sodium bicarbonate solution may give temporary relief. When the pruritus is restricted mainly to the abdomen—and it often is—an emollient such as lanoline cream gently rubbed into the skin each day is well worthy of trial.

Hirsutism

Q.—*What investigations are called for in a case of hirsutism? A woman of 28 has a growth of hair on her legs, slight growth on her chin, a tendency to masculine-type pubic hair, and hair round the nipples. Her menstrual history is normal, apart from slight irregularity and amenorrhoea for six months on starting nursing; there is no other evidence of endocrine imbalance. Is it possible to prescribe a depilatory cream which would relieve the hirsutism and, if so, could its use be continued indefinitely without danger?*

A.—The adrenogenital syndrome is usually said to consist of three features—hirsutism, adiposity, and amenorrhoea. Sometimes, instead of adiposity, one gets increased muscular development and strength, and even loss of adipose tissue. In this case the amenorrhoea would appear to be psychological, and should this be so we are probably dealing with a genetically determined hirsutism for which there is no medical or surgical endocrine treatment. In the case of adrenogenital syndrome the usual cause is bilateral hyperplasia of the adrenal cortex, and unilateral adrenalectomy may offer a modicum of relief. An adrenal or ovarian neoplasm is revealed by excessive secretion of 17-ketosteroids in the urine, and by intravenous pyelography or possibly pelvic examination, respectively. Depilatory creams are, in the writer's experience, fundamentally ineffective, and not without danger or severe discomfort. Other physical measures, such as shaving or electrolysis, are on the whole preferable.

NOTES AND COMMENTS

Salicyl-sulphonic Acid Test.—Dr. A. MICHAEL DAVIES (London, N.W.) writes: Under "Any Questions?" (December 3, p. 1306) the use of the salicyl-sulphonic acid test for the detection of "albumin" in urine is discussed and the statement made "that the test is not so delicate as the boiling test. . . ." Some months ago I had occasion to investigate this point and found the converse to be true—i.e., that the sulphosalicylic acid test is twice as sensitive as the boiling test in the detection of protein (*not* "albumin") in urine. A series of dilutions of plasma in urine were made, commencing at 0.5% and running down to 0.005%. The urine was fresh, pooled, and found to be free from protein and other abnormalities. The plasma was human, citrated and pooled, and was found to contain 7.0 g. of total proteins per 100 ml. (biuret method). Each test was performed in triplicate by each of three experienced laboratory technicians and myself, the operator having no prior knowledge of the protein content of the specimen, and the end-point taken to be the faintest detectable (naked eye) opalescence. The results showed close agreement. With 25% sulphosalicylic acid the end-point was reached at 0.04% plasma (a protein content of 2.8 mg. per 100 ml.) and with the boiling test and addition of 2% or 4% acetic acid the end-point was 0.08% plasma, a protein content of 5.6 mg. per 100 ml. The ease and sensitivity of the salicyl-sulphonic acid test make it eminently suitable for surgery or bedside use, and it deserves to be more widely employed. The possibility of false reactions with uric acid and "uroselectan" in no way detracts from its value, and a further point in its favour is the fact that it can be made into a quantitative test by using constant volumes and comparing with a set of standards. I have used it as the routine test for proteinuria in several clinical laboratories with complete success.

The Symptoms of Botulism.—Dr. GERALD LEIGHTON (Ramsey, Isle of Man) writes: In a typical outbreak usually several people are affected. All present the same symptoms within a few hours of each other, varying in severity; all remain for a time unaware of having taken the toxin, and go about as usual. There are no symptoms at all until the patient suddenly complains of dizziness and double vision, when paralysis of the ocular muscles is commencing. This may appear at any time from six hours to about thirty hours; having appeared, the outlook is serious. In a typical case there is no incubation stage with preliminary feverishness; the temperature is slightly subnormal. There is no pain, or only slight pains, no headache, slight vomiting in some cases, none in about half. Then appears the striking sign of more or less complete ptosis. Vision is not impaired. The speech becomes blurred and indistinct; attempts to walk are marked by staggering. There is no pain at this or at any other stage in a typical case. Consciousness remains to the end. As a rule there is obstinate constipation all the time, but no headache nor any rise of temperature. The later symptoms then develop: difficulty in swallowing; the larynx becomes paralysed; power of speech is often completely lost. The mental faculties are fully active and communication is achieved by writing. There is dyspnoea from accumulation of mucus. Lastly the intercostal muscles and diaphragm become paralysed and the circulation fails. Up to this point there is no marked deviation of the pulse from normal.

High-pitched Voice in Adult Male.—Mr. M. VIASTO (Westerham, Kent) writes: I was surprised to read the reply ("Any Questions?" November 26, p. 1246) to the question about high-pitched voice in adult male. The eunuchoid type of voice is heard now and again by laryngologists and speech therapists, who know little or nothing about the "secretions of androgens." In my experience the great majority of such cases have a psychological background and are amenable to therapy along well-established lines. . . .

Correction.—Dr. Terence East's *Failure of the Heart and Circulation* is priced 8s. 6d., not 6s. as stated in our recent review.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London*. ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.) TELEPHONE: EUSTON 2111. TELEGRAMS: *Britmedads, Westcent, London*.

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 2111. TELEGRAMS: *Medisecra, Westcent, London*.

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.